NOVARTIS

Galvus®

Composition

Active substance: Vildagliptin

Excipients: Lactose anhydrous, microcrystalline cellulose, sodium starch glycolate, magnesium stearate.
Information might differ in some countries.

Pharmaceutical form and quantity of active substance per unit

Tablets containing 50 mg vildagliptin

Indications/Potential uses

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
- in dual combination
- with metformin when diet, exercise and metformin alone do not result in adequate glycaemic control
- with a sulphonylurea (SU) when diet, exercise and a sulphonylurea alone do not result in adequate glycaemic control
- with a thiazolidinedione (TZD) when diet, exercise and a thiazolidinedione alone do not result in adequate glycaemic control
- in triple combination
- with metformin and a sulphonylurea when diet and exercise plus dual therapy with these agents do not result in adequate glycaemic control

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

Dosage/Administration

The dosage of antidiabetic therapy should be individualized.
The recommended dose of Galvus, when used as monotherapy, is 50 mg once or twice daily.
The recommended dose of Galvus, when used in combination with insulin (with or without metformin), is 50 mg once or twice daily, depending on renal function (see **"Patients with renal impairment"**).
The recommended dose of Galvus, when used in combination with metformin or in combination with metformin and a sulphonylurea, is 50 mg twice daily.
The recommended dose of Galvus, when used in combination with a sulphonylurea or a thiazolidinedione, is 50 mg once daily.
When used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia.
A dosage higher than 50 mg twice daily is not recommended.
The tablets can be taken with or without food.

Patients with renal impairment
No dosage adjustment of Galvus is required in patients with mild renal impairment (creatinine clearance [CrCl] ≥50 ml/minute, corresponding to serum creatinine levels <150 µmol/litre in men and ≤133 µmol/litre in women). The recommended dose in patients with moderate to severe renal impairment is 50 mg once daily (see **"Warnings and precautions"** and **"Pharmacokinetics"**).

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

Elderly patients
No dosage adjustment is required in elderly patients.

Children and adolescents
The safety and efficacy of Galvus have not been studied in patients under 18 years of age; therefore, the use of Galvus in children and adolescents is not recommended.

Contraindications

Hypersensitivity to vildagliptin or to any of the excipients.

Warnings and precautions

Management of diabetes should always also include diet control. Caloric reduction, weight loss and exercise are essential for the proper treatment of diabetic patients. This is true not only for pharmacotherapy but also as an adjunct to drug therapy.
Galvus should not be used in patients with type 1 diabetes or in patients with ketoacidosis.

Renal impairment
There is limited experience in patients with end-stage (end stage renal disease [ESRD]) on haemodialysis. Galvus should therefore be used with caution in these patients.
Creatinine clearance must be checked before the start of treatment and at regular intervals during treatment.

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

Liver enzyme monitoring
Cases of hepatic dysfunction (including rare cases of hepatitis) have been reported. In these cases, the patients were generally asymptomatic without clinical sequelae, and liver function test (LFT) results returned to normal after discontinuation of treatment. LFTs should be performed prior to the initiation of treatment with Galvus to determine the patient's baseline values. Hepatic function should be monitored during Galvus treatment at three-month intervals during the first year and periodically thereafter. In patients who develop increased transaminase levels, this test should be repeated. If the results of LFT are confirmed, the patient should be monitored at frequent intervals until test results return to normal. Withdrawal of Galvus is recommended in patients with elevated AST or ALT levels ≥3 x ULN.
Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue treatment with Galvus.
Following withdrawal of treatment with Galvus and normalization of LFT results, treatment with Galvus should not be reinitiated.

Pancreatitis
In post-marketing experience there have been spontaneously reported adverse reactions of acute pancreatitis. Patients should therefore be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain.
Resolution of pancreatitis has been observed after discontinuation of vildagliptin. If pancreatitis is suspected, vildagliptin and other potentially suspect medicinal products should be discontinued.

Heart failure
Experience with vildagliptin therapy in patients with New York Heart Association (NYHA) class III heart failure is limited. Vildagliptin should be used with caution in these patients. There is no experience of vildagliptin use in clinical trials in patients with NYHA functional class III-IV and therefore use is not recommended in these patients.

Skin disorders
Skin lesions, including blistering and ulceration, have been reported on the extremities of monkeys in nonclinical toxicology studies (see "Preclinical data"). Although no increased incidence of skin lesions was observed in clinical trials, there is only limited experience of patients with diabetic skin complications. Therefore, in keeping with routine care of diabetic patients, monitoring for skin disorders, such as blistering or ulceration, is recommended.

Hypoglycaemia
Patients receiving vildagliptin in combination with a sulphonylurea or insulin may be at increased risk of hypoglycaemia. A lower dose of sulphonylurea or insulin should therefore be considered in order to reduce the risk of hypoglycaemia.
Galvus tablets contain lactose. Patients with rare hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not take Galvus tablets.

Interactions

Since vildagliptin neither inhibits nor induces CYP450 enzymes, it is not likely to interact with co-medications that are metabolized by CYP450 or that act as inhibitors or inducers of these enzymes.
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

Pregnancy
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. Vildagliptin was not teratogenic in either rats or rabbits. There are, however, no adequate and well-controlled studies in pregnant women, and therefore vildagliptin should not be used during pregnancy unless clearly necessary.
Animal studies are not always predictive of human response. Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin monotherapy be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Lactation
As it is not known whether vildagliptin is excreted in breast milk, Galvus should not be administered to breastfeeding women. Studies in lactating rats have shown excretion in milk.

Effects on ability to drive and use machines

There have been no studies of the effects of this product on the ability to drive or use machines. Patients who experience dizziness should thus avoid driving vehicles or using machines.

Adverse effects

In controlled trials of over 12 weeks' duration that continued for up to 2 years, safety data were obtained from 2264 patients given Galvus as monotherapy and 1520 patients given Galvus as add-on therapy.
Elevations in transaminases were reported in clinical trials. Their severity was dose-dependent.
Rare cases of angioedema were reported with vildagliptin at a similar rate to the control group. A greater proportion of cases was reported when vildagliptin was administered in combination with an ACE inhibitor. The majority of the events were mild in severity and resolved with ongoing vildagliptin treatment.
In comparative controlled monotherapy studies, hypoglycaemia was uncommon.
Adverse effects reported in patients who received Galvus in double-blind studies as monotherapy and add-on therapy are listed below by system organ class and absolute frequency. Frequencies are defined as follows:

Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10 000 to <1/1000), very rare (<1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse effects are ranked in order of decreasing seriousness.

Infections and infestations
Very rare: Upper respiratory tract infections, nasopharyngitis.

Nervous system disorders
Common: Dizziness, tremor.
Uncommon: Headache, fatigue.

Vascular disorders
Uncommon: Peripheral oedema (*common* when Galvus is combined with a TZD).

Gastrointestinal disorders
Common: Nausea.
Uncommon: Constipation.

Hepatic disorders
Rare: Elevated transaminase levels.

Musculoskeletal disorders
Uncommon: Arthralgia.

Metabolism disorders
Uncommon: Hypoglycaemia (*common* in combination therapy with metformin or a sulphonylurea), weight increase (*common* when Galvus is combined with a TZD).

General disorders
Uncommon: Asthenia.

Post-marketing experience
The following additional adverse drug reactions have been reported during the post-marketing period: Rare cases of hepatitis that resolved following discontinuation of Galvus (see **"Warnings and precautions"**).
Frequency not known: Urticaria, pancreatitis, bullous eruptions, localized exfoliation or blistering of the skin.

Combination of vildagliptin with insulin (with/without metformin)
The incidence of hypoglycaemia in the controlled clinical studies conducted was similar in both treatment groups (14.0% of patients on vildagliptin vs. 16.4% of patients on placebo). Severe hypoglycaemia occurred in n = 2 patients on vildagliptin vs. n = 6 on placebo. The overall effect on mean weight was small in both treatment groups (+0.6 kg on vildagliptin vs. ±0 kg on placebo).

The following adverse effects occurred in these studies:

Metabolism and nutrition disorders
Common: Decreased blood glucose.

Nervous system disorders
Common: Headache, chills.

Gastrointestinal disorders
Common: Nausea, gastro-oesophageal reflux disease.

Uncommon: Diarrhoea, flatulence.
Discontinuations due to these adverse effects were rare overall.

Combination with metformin and a sulphonylurea
Hypoglycaemia was common in both treatment groups (5.1% for vildagliptin + metformin + glimepiride vs. 1.9 % for placebo + metformin + glimepiride). No severe hypoglycaemic event was reported in the vildagliptin group. At the end of the study, the effect on mean body weight was small (+0.6 kg in the vildagliptin group and 0.1 kg in the placebo group).

Adverse effects in patients who received Galvus 50 mg twice daily in combination with metformin and a sulphonylurea (n = 1579):

Metabolism and nutrition disorders
Common: Hypoglycaemia.

Nervous system disorders
Common: Dizziness, tremor.

Skin disorders
Common: Hyperhidrosis.

General disorders
Common: Asthenia.

Overdose

Oedema and muscle pain were dose-limiting in clinical trials. At 600 mg, one subject developed oedema of the hands and feet, and an excessive increase in creatine phosphokinase (CPK) levels, accompanied by elevated levels of aspartate aminotransferase (AST), C-reactive protein and myoglobin. Three additional subjects in this group presented with oedema of both feet, accompanied by paraesthesia in two cases. All symptoms and laboratory abnormalities resolved after study-drug discontinuation.
In case of overdose, Galvus should be withdrawn and the patient should be given symptomatic and supportive treatment.
Galvus is not dialyzable; however, the major hydrolysis metabolite can be removed by haemodialysis.

Properties/Actions

ATC code: A10BH02

Mechanism of action/Pharmacodynamics
Vildagliptin is a dipeptidyl-peptidase-4 (DPP-4) inhibitor.
Administration of vildagliptin inhibits 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 50 to 100 mg vildagliptin daily in patients with type 2 diabetes significantly improved markers of beta cell function, including HOMA (Homeostasis Model Assessment-β), proinsulin to insulin ratio and measures of beta cell responsiveness from the frequently sampled oral glucose tolerance test in non-diabetic (normoglycaemic) individuals, vildagliptin does not stimulate insulin secretion or reduce glucose in normal subjects.
By increasing endogenous GLP-1 levels, vildagliptin enhances the sensitivity of alpha cells to glucose, resulting in more glucose-appropriate glucagon secretion.
Administration of vildagliptin in the insulin/glucagon ratio during hyperglycaemia due to increased incretin hormone levels results in a decrease in fasting and 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.

Clinical efficacy
Monotherapy (metformin naive)
Two 24-week, double-blind, placebo-controlled trials were carried out in treatment-naive patients with type 2 diabetes. In these studies, administration of 50 mg vildagliptin once daily resulted in mean changes from baseline in HbA_{1c} (-0.8% and -0.5%) that were statistically significant compared with placebo.
In addition, vildagliptin monotherapy was compared to metformin, rosiglitazone or pioglitazone in several studies in treatment-naive patients. The patients had had diabetes for an average of two years. In these studies, vildagliptin showed a clinically relevant reduction in HbA_{1c} as compared with baseline. Non-inferiority was statistically demonstrated as compared with rosiglitazone, but not as compared with metformin and pioglitazone.
In a two-year long-term trial, 50 mg vildagliptin twice daily was compared with daily doses of up to 320 mg gliclazide. After two years, mean reductions in HbA_{1c} were 0.5% with vildagliptin and 0.6% with gliclazide. There was less weight gain with vildagliptin (-0.75 kg) and fewer hypoglycaemic episodes (0.7%) than with gliclazide (1.6 kg and 1.7%, respectively).

Combination therapy
In patients pretreated with oral antidiabetics, combination therapy trials were carried out with metformin (two studies, n = 1091), with SUs (sulphonylureas (n = 408) and glitazones (n = 398). Patients in these studies had had diabetes for an average of 7.4 years.
The combination study with metformin included only patients with an initial dose of 2000 mg or more. 50 mg vildagliptin once or twice daily in combination with 2000 mg metformin was more effective than metformin alone; the difference with vildagliptin was -0.7% and -1.1%, with high significance. In the smaller Phase II study (2204) also, the combination of 50 mg vildagliptin once daily with 1500 mg metformin led to -0.65%, significantly better than metformin alone.
Patients achieving inadequate glycaemic control on sulphonylurea monotherapy were included in the combination trial with glimepiride. They are documented as having been given at least the normal dose in each case (at least 4 mg) and not been pretreated with 4 mg glimepiride). The combination of 50 mg vildagliptin once daily with 4 mg glimepiride was significantly better than 4 mg glimepiride alone, with a difference in HbA_{1c} of -0.64%.
In the combination trial in patients pretreated with glitazones, the combination of 50 mg vildagliptin once or twice daily with 45 mg pioglitazone was significantly better than 45 mg pioglitazone alone. The difference in HbA_{1c} was -0.6 and -0.67.
In a 24-week trial in patients whose blood glucose was inadequately controlled with metformin (≥1500 mg) monotherapy, 50 mg vildagliptin twice daily was compared with 30 mg pioglitazone once daily. Mean reductions from baseline HbA_{1c} (8.4%) were 0.9% with vildagliptin added to metformin and 1.0% with pioglitazone added to metformin. For baseline HbA_{1c} >9.0%, the decrease was greater (1.5%) in both treatment groups. Patients receiving pioglitazone in addition to metformin experienced an increase in weight of 1.9 kg. Those receiving vildagliptin in addition to metformin gained 0.3 kg in weight.
In a long-term trial lasting up to two years, 50 mg vildagliptin twice daily was compared with up to 6 mg glimepiride once daily in patients treated with metformin. After two years, mean reductions in HbA_{1c} were 0.06% with the vildagliptin/metformin combination and 0.14% with glimepiride/metformin. Body weight change with vildagliptin was -0.2 kg vs. +1.2 kg with glimepiride. The incidence of hypoglycaemic episodes was significantly lower in the vildagliptin group (2.3%) than in the glimepiride group (18.2%).
In a 52-week trial, vildagliptin (50 mg twice daily) was compared with gliclazide (mean daily dose: 229.5 mg) in patients inadequately controlled with metformin (metformin dose at baseline: 1928 mg daily). After one year, mean reductions in HbA_{1c} were 0.81% with vildagliptin added to metformin and 0.66% with gliclazide added to metformin (mean gliclazide added to metformin (mean baseline HbA_{1c}: 8.5%), meaning that 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 of vildagliptin (50 mg once daily), the mean reduction in HbA_{1c} was -0.74% from a mean baseline of 7.9% in patients with moderate renal impairment and -0.43% from a mean baseline of 7.7% in patients with severe renal impairment. Placebo decreased HbA_{1c} by 0.21% and 0.32% in patients with moderate and severe renal impairment, respectively, from similar mean baseline values. The HbA_{1c} reduction with vildagliptin was statistically significantly larger than with placebo. 68.6% and 80.5% of patients with moderate and severe renal impairment, respectively, were additionally treated with insulin. The mean daily doses were 26 units and 31.6 units, respectively.
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 or without metformin. Vildagliptin in combination with insulin significantly decreased HbA_{1c} compared with placebo: In the overall population, the placebo-adjusted reduction from a mean baseline HbA_{1c} 8.8% was -0.72%. Hypoglycaemia occurred in 8.4% and 7.2% of patients treated with vildagliptin and placebo, respectively. The patients' mean weight showed little overall change (+0.2 kg on vildagliptin and -0.7 kg on placebo).
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 (≥1500 mg daily) and glimepiride (≥4 mg daily). Vildagliptin in combination with metformin and glimepiride significantly decreased HbA_{1c} compared with placebo: the placebo-adjusted mean reduction from a mean baseline HbA_{1c} of 8.8% was -0.76%.

Pharmacokinetics

Linearity
Vildagliptin is rapidly absorbed with an oral bioavailability of 85%.

Absorption
Vildagliptin is rapidly absorbed with peak plasma concentrations reached after about 1 hour. Ingestion of food has no relevant effect on absorption. Food does not alter 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 litres.

Metabolism
Vildagliptin is largely metabolized (69% of the dose), partly by DPP-4. The major metabolite, LAY151 (57% of the dose), which is formed by hydrolysis, is inactive. There is also an amide hydrolysis product (4% of the dose). Vildagliptin is not metabolized by cytochrome P450 enzymes.

Elimination
85% of the dose is excreted in the urine and 15% of the dose is recovered in the faeces. Unchanged vildagliptin accounts for 23% of the dose. The elimination half-life is approximately 3 hours.

Pharmacokinetics in special patient populations
No differences in the pharmacokinetics of vildagliptin have been observed between men and women.

Elderly patients
Plasma concentrations are elevated in patients over 70 years of age. However, the change in exposure to vildagliptin is not clinically relevant.

Hepatic impairment
Exposure to vildagliptin (100 mg) was not elevated after a single dose of 100 mg in patients with mild hepatic impairment. In patients with moderate hepatic impairment, exposure was increased by 22% (68% upper CI limit).

Renal impairment
In a pharmacokinetic study, vildagliptin AUC increased on average 1.4-, 1.7- and 2-fold in patients with mild, moderate (CrCl 30 to <50 ml/minute), moderate (CrCl 30 to <50 ml/minute) and severe (CrCl <30 ml/minute) renal impairment, respectively, compared to healthy subjects. AUC of the metabolites LAY151 and BQS867 increased on average 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 AUC and C_{max} were 1.8-7 and 14-fold higher, respectively, than in patients with normal renal function.
Vildagliptin was removed by haemodialysis to a limited extent (3% over a 3- to 4-hour haemodialysis session starting 4 hours post dose).

Children
The pharmacokinetics have not been studied.

Preclinical data

In a distribution study in rats, concentrations measured in kidney and liver tissue were 10-30 times higher than concentrations in the plasma.
At *in vitro* concentrations and dog *in vivo* plasma concentrations that markedly exceeded C_{max}-based exposure levels in humans given 50 mg vildagliptin (80-260 times higher for the *in vitro* findings and 43 times higher for the *in vivo* findings), an inhibitory action on cardiac sodium channels, a decreased rate of depolarization in Purkinje fibres, slowed conduction in isolated rabbit hearts and a widening of the QRS complex in the ECG of dogs were observed.
A two-year carcinogenicity study was conducted in rats at oral doses up to 900 mg/kg (approximately 370 times human AUC exposure at 50 mg). No increases in tumour incidence attributable to vildagliptin were observed. A two-year carcinogenicity study was conducted in mice at oral doses up to 1000 mg/kg (up to 420 times human AUC exposure at the 50 mg dose). The incidence of mammary tumours was increased in female mice at a dose approximately 260 times higher than the human dose of 50 mg vildagliptin; mammary tumours were not more frequent at approximately 100 times the human exposure. The incidence of haemangiosarcoma was increased in male mice at AUC exposure levels ≥74 times the human dose of 50 mg vildagliptin, and in female mice at around 260 times the human exposure. No statistical increase in the incidence of haemangiosarcoma was observed in males at approximately 27 times the human exposure, and in females at 74 times or at approximately 100 times the human exposure.
Vildagliptin was not mutagenic in a variety of mutagenicity tests including a bacterial reverse mutation (Ames) assay and a human lymphocyte chromosomal aberration assay. An oral bone marrow micronucleus test in both rats and mice did not reveal clastogenic or aneugenic effects up to 2000 mg/kg, or approximately 2000 times the human dose. An *in vivo* mouse liver comet assay using the same dose was also negative.
In a 13-week toxicity study in cynomolgus monkeys, skin lesions were recorded at doses ≥5 mg/kg/day. These lesions were confined to the extremities (hands, feet, ears and tail).
At 5 mg/kg/day (AUC-based exposure slightly higher than human exposure at the 50 mg dose), only blisters were observed. These were reversible despite continued treatment, and were not associated with histopathological abnormalities.
Blisters, skin peeling, loss of tail sores in connection with histopathological changes were noted at doses above 20 mg/kg/day (approximately 5 times human AUC exposure at the 50 mg dose).
Necrotic lesions of the tail were observed at ≥80 mg/kg/day.
Skin lesions were reversible (up to at least 80 mg/kg) if administration was stopped before necrosis occurred.
Skin lesions have not been observed in humans or in other species given vildagliptin.

Other information

Shelf life
Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage
Do not store above 30°C. Protect from moisture and store in the original pack.
Keep out of the reach of children.

Pack sizes

Country specific pack sizes.

Manufacturer

See folding box.

Information last revised

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® = registered trademark
Novartis Pharma AG, Basle, Switzerland

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists