

GALVUS

(vildagliptin)

50 mg Tablet

Name of the medicinal product

Galvus 50 mg tablet

Qualitative and quantitative composition

Vildagliptin : 1-[(3-Hydroxy-adamant-1-ylamino)-acetyl]-pyrrolidine-2(S)-carbonitrile.

One tablet of Galvus contains 50 mg of vildagliptin.

Pharmaceutical form

Galvus 50 mg : white to light yellowish, round (8 mm diameter), tablet. One side is debossed with "NVR", and the other side with "FB".

Clinical particulars

Therapeutic indications

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

- as monotherapy.
- in dual combination with metformin, a sulphonylurea (SU), a thiazolidinedione (TZD) when diet, exercise and a single antidiabetic agent do not result in adequate glycaemic control.

Posology and method of administration

The management of antidiabetic therapy should be individualized.

Monotherapy:

The recommended dose of Galvus 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.

Combination therapy:

Combination therapy with other antidiabetic drugs such metformin, an SU, a TZD may be given if a tighter glycaemic control is required on the top of the maximum recommended daily dose of 100 mg Galvus monotherapy.

The recommended dose of Galvus is 50 mg or 100 mg daily in dual combination with metformin, an SU, or a TZD. The 50 mg dose should be administered once daily in the morning. The 100 mg dose should be administered as two divided dose of 50 mg given in the morning and evening.

When used in dual combination with a sulphonylurea, 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.

Galvus can be administered with or without meal.

Patients with hepatic or renal impairment

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

In patients with mild renal impairment, the recommended dose of Galvus is 50 mg once daily in the morning or 50 mg twice daily given in the morning and evening. Galvus is, however, not recommended in patients with moderate or severe renal impairment or End Stage Renal Disease (ESRD) on haemodialysis (see also sections Special warnings and precautions for use and Pharmacokinetic properties under Special Populations).

There is limited data on the use of combination therapy in patients with renal and hepatic impairment. Therefore, the use of Galvus is not recommended in these patients.

Elderly patients

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

Paediatric patients

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

Contraindications

Galvus is contraindicated in patients with known hypersensitivity to vildagliptin or to any of the excipients. Galvus is contraindicated in patients with moderate and severe renal impairment and hepatic impairment.

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 moderate or severe renal impairment and in patients with End Stage Renal Disease (ESRD) on haemodialysis. Therefore, the use of Galvus is not recommended in these patients.

Hepatic impairment

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

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 Galvus. Galvus is not recommended in patients with a pre-treatment ALT or AST >2.5X the upper limit of normal. LFTs should be monitored during Galvus treatment at three-month intervals during the first year and periodically thereafter.

Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of 3X upper limit of normal or greater persist, withdrawal of therapy with Galvus is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Galvus and contact their physician immediately. Following withdrawal of treatment with Galvus and LFT normalisation, vildagliptin treatment should not be reinitiated.

Other

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

Interaction with other medicinal products and other forms of interaction

Vildagliptin has a low potential for drug interactions. Since vildagliptin is not a cytochrome P (CYP) 450 enzyme substrate nor does it inhibit nor induces CYP 450 enzymes, it is not likely to interact with co-medications that are substrate, inhibitors or inducers of these enzymes.

Furthermore, vildagliptin does not affect metabolic clearance of co-medications metabolised by CYP 1A2, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1, and CYP 3A4/5. Drug-drug interaction studies were conducted with commonly co-prescribed medications for patients with type 2 diabetes or medications with a narrow therapeutic window. As a result of these studies no clinically relevant interactions with other oral antidiabetics (glibenclamide, pioglitazone, metformin, amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin) were observed after co-administration with vildagliptin.

Pregnancy and 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 the benefit to the mother outweighs the potential risk to the foetus.

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 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 human milk Galvus should not be administered to breast feeding women.

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.

Undesirable effects

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 received 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, 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 [50]. In data from controlled monotherapy and add-on therapy trials up to 24 weeks in duration the incidence of ALT or AST elevations \geq 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 50mg 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 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 (\geq 1/10); common (\geq 1/100, <1/10); uncommon (\geq 1/1,000, <1/100); rare ($>$ 1/10,000 to \leq 1/1,000); very rare (\leq 1/10,000). 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 50 mg 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 1,373) of patients treated with

vildagliptin 50 mg twice daily compared to 0.2% (2 of 1,082) of patients in the groups treated with an active comparator or placebo, with no serious or severe events reported.

Galvus is weight neutral when administered as monotherapy.

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

Nervous system disorders	
Common	Dizziness
Uncommon	Headache
Gastrointestinal disorders	
Uncommon	Constipation, nausea, diarrhea
General disorders and administration site conditions	
Uncommon	Oedema peripheral
Infection and infestation	
Common	Nasopharyngitis
Cardiovascular disorders	
Common	Hypertension

Combination with metformin

In clinical trials with the combination of vildagliptin + metformin, 0.4% of patients withdrew due to adverse reactions in the vildagliptin 50 mg once daily + metformin treatment group, and no withdrawal due to adverse reactions was reported in either the vildagliptin 50 mg bid + metformin or the placebo + 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+metformin (0.4%). No severe hypoglycaemic events were reported in the vildagliptin arms.

Galvus is weight neutral when administered in combination with metformin.

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

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

Combination with a sulphonylurea

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

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

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

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

<u>Nervous system disorders</u>	
<u>Common</u>	<u>Tremor, headache, dizziness</u>
<u>General disorders and administration site conditions</u>	
<u>Common</u>	<u>Asthenia</u>

Combination with a thiazolidinedione

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

In clinical trials, no hypoglycaemia events were reported in patients receiving vildagliptin 50 mg once daily + pioglitazone 45 mg, hypoglycaemia was uncommon in patients receiving vildagliptin 50 mg twice daily + pioglitazone 45 mg (0.6%) but common in patients receiving placebo + pioglitazone 45 mg (1.9%). No severe 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 Galvus 50 mg daily and Galvus 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 4 Adverse reactions reported in patients who received Galvus 50 mg once daily (n= 146) or 50 mg twice daily (n=158) in combination with a thiazolidinedione in double-blind studies

<u>Investigations</u>	
<u>Common</u>	<u>Weight increase</u>
<u>Vascular disorders</u>	
<u>Common</u>	<u>Oedema peripheral</u>

Overdose

Signs and symptoms

In healthy subjects (seven to fourteen subjects per treatment group), Galvus was administered in once-daily doses of 25, 50, 100, 200, 400, and 600 mg for up to 10 consecutive days. Doses up to 200 mg were well tolerated. At 400 mg, there were three cases of muscle pain, and individual cases of mild and transient paraesthesia, fever, oedema and transient increase in lipase levels (2x ULN). 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. All symptoms and laboratory abnormalities resolved after study drug discontinuation.

Management

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

Pharmacological properties

Pharmacodynamic properties

Vildagliptin, a member of the islet enhancer class, is a potent and selective dipeptidyl-peptidase-4 (DPP-4) inhibitor that improves glycaemic control.

The administration of vildagliptin results in rapid and complete inhibition of DPP-4 activity. In patients with type 2 diabetes, administration of vildagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. 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).

By increasing the endogenous levels of these incretin hormones, vildagliptin enhances the sensitivity of beta cells to glucose resulting in improved glucose-dependent insulin secretion. Treatment with 50 to 100 mg daily in patients with type 2 diabetes significantly improved markers of beta cell function. The degree of improvement in beta-cell function is dependent on the initial degree of impairment; in non-diabetic (normal 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 more glucose-appropriate glucagon secretion. The reduction in inappropriate glucagon during meals in turn attenuates insulin resistance.

The enhanced increase in the insulin/glucagon ratio during 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. In addition, a reduction in postprandial lipaemia that is not associated with vildagliptin's incretin mediated effect to improve islet function, has been observed.

Clinical Experience

A total 5,795 patients with type 2 diabetes participated in 13 double-blind, placebo- or active controlled clinical trials of at least 12 week treatment duration. In these studies, vildagliptin was administered to 3,784 patients at daily doses of 50 mg once daily (n=1,102), 50 mg twice daily (n=2,027) or 100 mg once daily (n=655). The number of male and female patients receiving vildagliptin 50 mg once daily or 100 mg daily was 2,069 and 1,715, respectively. The number of patients receiving vildagliptin 50 mg once daily or 100 mg daily who were ≥ 65 years of age was 664 and 121 of the patients were ≥ 75 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 glycaemic control when given as monotherapy or when used in combination with metformin, a sulphonylurea, and a thiazolidinedione, as measured by clinically relevant reductions in HbA_{1c} from baseline at study endpoint (see Table 5).

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

In a 52-week trial (LAF2309), vildagliptin (100 mg/day) reduced baseline HbA_{1c} by -1% compared to -1.4% 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 trial (LAF2327), vildagliptin (100 mg/day) was compared to rosiglitazone (8 mg once daily). Mean reductions were -1.1% with vildagliptin and -1.3% with rosiglitazone in patients with mean baseline HbA_{1c} of 8.7%. Patients receiving rosiglitazone experienced a mean increase in weight (+1.6 kg) while those receiving vildagliptin experienced no weight gain (-0.3 kg). The incidence of peripheral oedema was lower in the vildagliptin group than in the rosiglitazone group (2.1% vs. 4.1%, respectively).

Table 5 Key efficacy results of vildagliptin in placebo-controlled monotherapy trials and in add-on combination therapy trials (primary efficacy ITT population)

<u>Monotherapy placebo controlled studies</u>	<u>Mean baseline HbA_{1c} (%)</u>	<u>Mean change from baseline in HbA_{1c} (%) at week 24</u>	<u>Placebo-corrected mean change in HbA_{1c} (%) at week 24 (95%CI)</u>
<u>Study 2301: Vildagliptin 50 mg once daily (N=104)</u>	8.2	-0.8	-0.5*(-0.8, -0.1)
<u>Study 2301: Vildagliptin 50 mg twice daily (N=90)</u>	8.6	-0.8	-0.5*(-0.8, -0.1)
<u>Study 2384: Vildagliptin 50 mg once daily (N=84)</u>	8.3	-0.5	-0.5*(-0.9, -0.1)
<u>Study 2384: Vildagliptin 50 mg twice daily (N=79)</u>	8.4	-0.7	-0.7*(-1.1, -0.4)

		<u>* p<0.05 for comparison versus placebo</u>	
<u>Add-on / Combination studies</u>			
<u>Study 2303: Vildagliptin 50 mg once daily + metformin (N=143)</u>	<u>8.4</u>	<u>-0.5</u>	<u>-0.7*(-1.0, -0.5)</u>
<u>Study 2303: Vildagliptin 50 mg twice daily + metformin (N=143)</u>	<u>8.4</u>	<u>-0.9</u>	<u>-1.1*(-1.4, -0.8)</u>
<u>Study 2305: Vildagliptin 50 mg daily + glimepiride (N=132)</u>	<u>8.5</u>	<u>-0.6</u>	<u>-0.6*(-0.9, -0.4)</u>
<u>Study 2304: Vildagliptin 50 mg daily + pioglitazone (N=124)</u>	<u>8.6</u>	<u>-0.8</u>	<u>-0.5*(-0.7, -0.2)</u>
<u>Study 2304: Vildagliptin 50 mg twice daily + pioglitazone (N=136)</u>	<u>8.7</u>	<u>-1.0</u>	<u>-0.7*(-0.9, -0.4)</u>
		<u>* p<0.05 for comparison versus placebo + background therapy</u>	

Pharmacokinetic properties

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 (V_{ss}) 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

Gender

No differences in the pharmacokinetics of Galvus were observed between male and female subjects with a diverse range of age and body mass index (BMI). DPP-4 inhibition by Galvus was unaffected by gender.

Obesity

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

Hepatic Impairment

The effect of impaired hepatic function on the pharmacokinetics of Galvus 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 Galvus (100 mg) after a single dose in subjects with mild and moderate hepatic impairment was decreased (20% and 8%, respectively), while the exposure to Galvus for subjects with severe impairment was increased by 22%. The maximum change (increase or decrease) in the exposure to Galvus 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 Galvus.

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.

Renal Impairment

In subjects with mild, moderate, and severe renal impairment, and ESRD patients on haemodialysis, systemic exposure to vildagliptin was increased (C_{max} 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 renal impairment (AUC 1.6- to 6.7-fold). Changes in exposure to vildagliptin did not correlate with severity of renal impairment, whereas changes in exposure to the inactive metabolite did correlate. Elimination half-life of vildagliptin was not affected by renal impairment. No dosage adjustment is required in patients with mild renal impairment. Due to limited experience, the use of Galvus is not recommended in patients with moderate or severe renal impairment or in patients with ESRD on haemodialysis (see section Special warnings and precautions for use).

Elderly

In otherwise healthy elderly subjects (≥ 70 years), the overall exposure to Galvus (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 Galvus is not affected by age in the age groups studied.

Paediatric

No pharmacokinetic data available.

Ethnic Group

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

Preclinical safety data

A two-year carcinogenicity study was conducted in rats at oral doses up to 900 mg/kg (approximately 200 times the human exposure at the maximum recommended dose). No increases in 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 240 times the human exposure at the maximum recommended dose). Mammary tumour incidence was increased in female mice at approximately 150 times the maximum anticipated human exposure to vildagliptin; it was not increased at approximately 60 times the maximum human exposure. The incidence of haemangiosarcoma was increased in male mice treated at 42 to 240 times the maximum human exposure to vildagliptin and in female mice at 150 times the maximum human exposure. No significant increases in haemangiosarcoma incidences were observed at approximately 16 times the maximum human exposure to vildagliptin in males and approximately 60 times the maximum human exposure in females.

Vildagliptin was not mutagenic in a variety of mutagenicity tests including a bacterial reverse mutation Ames assay and a human lymphocyte chromosomal aberration assay. Oral bone marrow micronucleus tests in both rats and mice did not reveal clastogenic or aneugenic potential up to 2,000 mg/kg or approximately 400 times the maximum human exposure. An in-vivo mouse liver comet assay using the same dose was also negative.

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

Pharmaceutical particulars

Incompatibilities

Not applicable.

Special precautions for storage

Do not store above 30°C, protect from moisture.

Store in the original package. Galvus must be kept out of the reach and sight of children.

Nature and contents of container

Alu/Alu blister packs

Instructions for use and handling <and disposal>

No special requirements.

Package

Galvus® 50 mg Tablet: box, 1, 2, 3 Blister @ 14 Tablets;

HARUS DENGAN RESEP DOKTER

To be dispensed only on the prescription of a physician.

Manufactured by Novartis Pharma Stein AG, Stein, Switzerland for Novartis Pharma AG, Basel, Switzerland. Imported by PT Novartis Indonesia, Citeureup, Bogor, Indonesia.

