NOVARTIS

**Galvus 50 mg, tablet**

Vildagliptin 50 mg per tablet

Professional Information

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| Document status: | Final |
| Release date: | 15 May 2022 |

**Scheduling Status: S3**

## 1. Name of the medicine

Galvus 50 mg

## 2. Qualitative and Quantitative composition

Each tablet GALVUS 50 mg contains 50 mg vildagliptin

Contains sugar (lactose): 47.82 mg per tablet

## 3.Pharmaceutical form

GALVUS 50 mg: white to light yellowish, round, flat, bevelled edged 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 to improve glycaemic control in adult patients with type 2 diabetes mellitus, as add-on therapy, in combination with metformin, a sulphonylurea (SU), or insulin (with or without metformin) when diet, exercise and a single antidiabetic medicine do not result in adequate glycaemic control.

GALVUS is also indicated in triple combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicines do not provide adequate glycaemic control.

Management of diabetes should always include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient. This is important not only for the primary treatment of diabetes, but also as an adjunct to medicinal therapy.

**4.2 Posology and Method of administration**

The management of antidiabetic therapy should be individualised.

The recommended dose of GALVUS is 50 mg a day or 50 mg twice a day in combination with metformin or insulin (with or without metformin).

The recommended dose of GALVUS is 50 mg twice a day for triple combination with metformin and a SU.

When used in combination with a sulphonylurea, the recommended dose of GALVUS is 50 mg once daily administered in the morning. In this patient population, GALVUS 100 mg daily was no more effective than GALVUS 50 mg once daily.

**Patients with renal impairment:**

In patients with moderate or severe renal impairment or with End Stage Renal Disease (ESRD) on haemodialysis the recommended dose of GALVUS is 50 mg once daily (see section 5.2).
The maximum dose should be 50 mg in patients with mild renal impairment.

**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 without renal impairment (see section 5.2).

**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 section 5.2).

**4.3 Contraindications**

GALVUS is contraindicated in patients with known hypersensitivity to vildagliptin or to any of the excipients of GALVUS.

GALVUS is contraindicated in patients with hepatic impairment, including patients with a pre-treatment ALT or AST >2,5 X the upper limit of normal.

**4.4 Special warnings and precautions for use**

**Hepatic impairment:**

GALVUS is contraindicated in patients with hepatic impairment, including patients with a pre-treatment elevated ALT or AST (see section 4.3).

**Liver enzyme monitoring:**

**Cases of hepatic dysfunction (including hepatitis) have been reported. In these cases, the patients were generally asymptomatic and liver function tests (LFTs) returned to normal after discontinuation of treatment. LFTs should be performed prior to the initiation of treatment with GALVUS.**

**LFT-monitoring is imperative:**

**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 3 X upper limit of normal or greater persist, GALVUS should be discontinued.

Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue GALVUS and contact their medical practitioner immediately. Following withdrawal of treatment with GALVUS and LFT normalisation, GALVUS treatment should not be reinitiated.

**Heart Failure:**

A clinical trial of vildagliptin, as contained in Galvus, in patients with New York Heart Association (NYHA) functional class I-III showed that treatment with vildagliptin was not associated with a change in left-ventricular function or worsening of pre-existing congestive heart failure (CHF) versus placebo. Clinical experience in patients with NYHA functional class III treated with vildagliptin is still limited and results are inconclusive.

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.

GALVUS may cause arthralgia that can be severe.

**Severe cutaneous adverse reactions**

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome, erythema multiforme, acute generalised exanthematous pustulosis, erythroderma (generalised exfoliative dermatitis) and pemphigoid have been reported in patients treated with DPP-4 inhibitors including GALVUS. SCARs are regarded as a class effect of DPP-4 inhibitors such as GALVUS. If a patient develops SCAR, treatment with DPP-4 inhibitors such as GALVUS must immediately be discontinued and appropriate treatment instituted. Patients should continue with an alternative class of anti-diabetic medicines.

**Rhabdomyolysis**

Rhabdomyolysis has been reported during use of DPP-4 inhibitor containing products such as GALVUS. However, causality could not be assessed due to confounding factors such as concomitant use of medicines (statins, colchicine, etc.) or co-morbid conditions (Renal failure, hypovolemia, etc.), known to cause or predispose to development of rhabdomyolysis. Close monitoring of patients using DPP-4 inhibitor containing products in presence of predisposing risk factors is recommended.

**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.

GALVUS contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take GALVUS.

**4.5 Interaction with other medicines and other forms if interaction**

Vildigliptin as contained in GALVUS has a low potential for 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 substrates, inhibitors or inducers of these enzymes.

Furthermore, vildagliptin does not affect metabolic clearance of co-medications metabolised by CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5. Interaction studies were conducted with commonly co-prescribed medicines 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 GALVUS.

**4.6 Fertility, pregnancy and lactation**

GALVUS should not be used in pregnant and breastfeeding women, as safety in pregnancy and lactation has not been established.

Mothers on GALVUS should not breastfeed their infants.

**4.7 Effect on ability to drive and use machines**

GALVUS may cause dizziness. Patients who experience dizziness should avoid driving vehicles or using machines.

**4.8 Undesirable effects**

Safety data were obtained from 3 784 patients exposed to GALVUS in controlled trials of at least 12 weeks duration.

Cases of angioedema have been reported during treatment with GALVUS.

Cases of hepatic dysfunction (including hepatitis) have been reported. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function tests (LFTs) returned to normal after discontinuation of treatment. In data from controlled monotherapy and add-on therapy trials up to 24 weeks in duration, the incidence of ALT or AST elevations ≥ 3x ULN (classified as present on at least 2 consecutive measurements or at the final on-treatment visit) was 0,2 %, 0,3 % and 0,2 % for vildagliptin 50 mg daily, vildagliptin 50 mg twice daily and all comparators, respectively. These elevations in transaminases were generally asymptomatic, non-progressive in nature and not associated with cholestasis or jaundice.

Adverse reactions reported in patients who received GALVUS in double-blind studies as add-on therapy, 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). Within each frequency grouping, undesirable effects are presented in order of

decreasing seriousness.

Table 1: Adverse reactions reported in patients who received GALVUS 50 mg once daily (n=233) or 50 mg twice daily (n=183) in combination with metformin in double-blind studies, GALVUS 50 mg once daily in combination with a sulphonylurea in double-blind studies (n=170), GALVUS 50 mg twice daily in combination with insulin with or without metformin (n=371) and in combination with metformin and SU (n=157).

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| **Nervous system disorders** | |
| | Common: *Tremor, *dizziness, headache |
| ****General disorders and administration site conditions** | |
| | Common: Asthenia, peripheral oedema, ***chills |
| *****Gastrointestinal disorders** | |
| | Common: Nausea, gastroesophageal reflux disease, constipation |
| | Uncommon: Diarrhoea, flatulence |
| *****Investigations** | |
| | Common: Decreased blood glucose |
| **Metabolism and nutritional disorders** | |
| | Common: **** Hypoglycaemia |
| ****** Skin and subcutaneous tissue disorders:** | |
| | Common: Hyperhidrosis |

* GALVUS in combination with metformin and sulphonylurea only

** GALVUS in combination with sulphonylurea only

*** GALVUS in combination with insulin (with or without metformin)

****GALVUS in combination with metformin and sulphonylurea

In clinical trials with the combination of GALVUS + metformin, 0, 4 % of patients withdrew due to adverse reactions in the GALVUS 50 mg once daily + metformin, and no withdrawal due to adverse reactions was reported in either the GALVUS 50 mg twice daily + metformin or the placebo + metformin treatment groups.

In clinical trials, the incidence of hypoglycaemia was uncommon in patients receiving GALVUS 50 mg once daily in combination with metformin (0,9 %), patients receiving GALVUS 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 GALVUS arms.

In clinical trials, the incidence of hypoglycaemia when GALVUS 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 GALVUS arms.

**Post Marketing Experience:**

During post-marketing experience the following additional side effects have been reported:

- Cases of hepatitis, usually reversible upon medicine discontinuation (see section 4.4)
- Urticaria, bullous and exfoliative skin lesions, including bullous pemphigoid
- Pancreatitis
- Arthralgia, sometimes severe
- Rhabdomyolysis

Severe cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome, erythema multiforme, acute generalised exanthematous pustulosis, erythroderma (generalised exfoliative dermatitis) and pemphigoid have been reported in patients treated with DPP- 4 inhibitors including GALVUS.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

**4.9 Overdose**

**Signs and symptoms:**

Muscle pain, paraesthesia, fever and oedema have been reported. Increases in lipase levels (2x ULN), creatine phosphokinase (CPK) levels, accompanied by elevations of aspartate aminotransferase (AST), C-reactive protein, and myoglobin may develop.

**Management:**

Treatment is symptomatic and supportive.

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

**5 Pharmacological Properties**

Pharmacological Classification: A 21.2. Oral hypoglycaemics

**5.1 Pharmacodynamic properties**

Vildagliptin is a selective dipeptidyl-peptidase-4 (DPP-4) inhibitor.

It increases endogenous levels of the incretin hormones GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide) by inhibiting the enzyme responsible for their degradation, DPP-4 (dipeptidyl-peptidase-4). The incretin hormones GLP-1 and GIP enhance glucose-dependent insulin secretion and exhibit other antihyperglycaemic actions following their

release into the circulation from the gut in response to a meal. GLP-1 also suppresses inappropriate glucagon secretion. By increasing endogenous levels of these incretin hormones, vildagliptin enhances glucose-dependent insulin secretion by the pancreatic β-cell and suppresses inappropriately elevated glucagon secretion by the pancreatic α-cell.

The administration of vildagliptin results in a rapid and complete (>90 %) inhibition of DPP-4 activity. The duration of DPP-4 inhibition is dose-dependent. The mean residence time of DPP-4 inhibition after 50 mg and 100 mg once-daily dosing with vildagliptin is 8,3 hours and 9,6 hours, respectively. This inhibition in DPP-4 activity by vildagliptin is associated with increases in basal as well as meal-stimulated GLP-1 and GIP levels throughout the day. Vildagliptin improves pancreatic islet function as evidenced by the improved ability of the α-cell and β-cell to sense and respond to glucose.

**α-cell function:** An indication of α-cell function is the ability to suppress inappropriate glucagon secretion in the presence of hyperglycaemia. In type 2 diabetes, glucagon is inappropriately suppressed, resulting in increased hepatic glucose production. After a single oral dose of vildagliptin (100 mg qd) in patients with type 2 diabetes glucagon levels were reduced before the evening meal, both in the prandial period and throughout the overnight post-absorptive period relative to placebo.

**β-cell function:** An indication of β-cell function is glucose-dependent insulin secretion. Vildagliptin improves pancreatic β-cell responsiveness to glucose leading to increased insulin secretion. This effect occurs only in the presence of elevated glucose concentrations in patients with type 2 diabetes. In non-diabetic (normal glycaemic) individuals, vildagliptin does not stimulate insulin secretion nor does it reduce glucose levels.

**First phase insulin secretion:** An early and sensitive indicator of β-cell function is first phase insulin secretion in response to intravenous glucose. In untreated type 2 diabetes patients, first phase insulin secretion is virtually abolished, whereas patients treated with vildagliptin for 12 weeks demonstrated a clear improvement in restoration of first phase insulin secretion in response to a glucose stimulus.

After discontinuation of vildagliptin for 2 weeks, this improvement is diminished.

Vildagliptin inhibits hepatic glucose production during meals as well as during the overnight post-absorptive period. Furthermore, the improvements in glycaemic control are associated with attenuated insulin resistance.

In addition, vildagliptin reduces postprandial lipaemia reflecting an effect to decrease both chylomicron and VLDL triglycerides.

**5.2 Pharmacokinetic properties**

***Linearity:***

Vildagliptin is well 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 well absorbed with peak plasma concentrations observed at 1, 75 hours. Co-administration with food slightly decreases the rate of absorption of vildagliptin, as characterized by a 19 % decrease in peak concentrations, and a delay in the time to peak plasma concentration to 2,5 hours. There is no change in the extent of absorption, and food does not alter the overall exposure (AUC).

***Distribution:***

The plasma protein binding of vildagliptin is low (9,3 %), and vildagliptin distributes equally between plasma and red blood cells. The mean volume of distribution of vildagliptin at steady-state after intravenous administration (Vss) is 71 L, suggesting extravascular distribution.

***Metabolism:***

Metabolism is the major elimination pathway for vildagliptin in humans, accounting for 69 % of the dose. The major metabolite, LAY151, is pharmacologically inactive and is the hydrolysis product of the cyano moiety, accounting for 57 % of the dose, followed by the amide hydrolysis product (4 % of the dose). DPP-4 contributes partially to the hydrolysis of vildagliptin as shown in an in-vivo study using DPP-4 deficient rats. Vildagliptin is not metabolised 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:***

Although exposure in women was 13 % higher than in men, no statistically significant differences in the pharmacokinetics of vildagliptin were observed between male and female subjects with a diverse range of age and body mass index (BMI), DPP-4 inhibition by vildagliptin was unaffected by gender.

***Obesity:***

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

***Hepatic impairment:***

The effect of impaired hepatic function on the pharmacokinetics of vildagliptin was studied in subjects with mild, moderate, and severe hepatic impairment based on the Child-Pugh scores (ranging from 6 for mild to 12 for severe) in comparison to subjects with normal hepatic function. The exposure to vildagliptin (100 mg) after a single dose in subjects with mild and moderate hepatic impairment was decreased (20 % and 8 %, respectively), while the exposure to vildagliptin for subjects with severe impairment was increased by 22 %. The maximum change (increase or decrease) in the exposure to vildagliptin is ~30 %, which is not considered to be clinically relevant. There was no correlation between the severity of hepatic function impairment and changes in exposure to vildagliptin.

The use of vildagliptin is not recommended in patients with hepatic impairment including patients with a pre-treatment ALT or AST >2,5X the upper limit of normal (see section 4.3).

***Renal impairment:***

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 increased 1,6, 3,2 and 7,3-fold and that of BQS867 increased 1,4, 2,7 and 7,3-fold in patients with mild, moderate and severe renal impairment, respectively, compared to healthy volunteers. Limited data from patients with end stage renal disease (ESRD) indicate that vildagliptin exposure is similar to that in patients with severe renal impairment. LAY151 concentrations in ESRD patients were approximately 2-3-fold higher than in patients with severe renal impairment. Dosage adjustment may be required in patients with renal impairment. (see section 4.2).

Vildagliptin was removed by haemodialysis to a limited extent (3 % over a 3-4 hour haemodialysis session starting 4 hours post dose).

***Elderly:***

In otherwise healthy elderly subjects (≥ 70 years), the overall exposure to vildagliptin (100 mg once daily) was increased by 32 % with an 18 % increase in peak plasma concentration compared to

younger healthy subjects (18-40 years). These changes are not considered to be clinically relevant.

DPP-4 inhibition by vildagliptin is not affected by age in the age groups studied.

***Paediatric:***

No pharmacokinetic data available.

## 6 Pharmaceutical Particulars

### 6.1 List of excipients

Lactose anhydrous; microcrystalline cellulose; sodium starch glycolate and magnesium stearate.

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

36 Months

### 6.4 Special precautions for storage

Store at or below 30 °C in the original package. Protect from moisture.

Do not remove blister from carton until required for use.

Keep out of the reach of children.

### 6.5 Nature and contents of container

28 or 56 tablets in PA/Al/PVC (polyamide/aluminium/polyvinylchloride) blisters with an aluminium foil backing. Not all pack sizes may be marketed.

The blister foil is imprinted with the proprietary name, company name, batch number and expiry date.

**6.6 Special precautions for disposal**

Not Applicable

**7 Holder of certificate of registration**

Novartis South Africa (Pty) Ltd.

Magwa Crescent West,

Waterfall City

Jukskei View,

Johannesburg

2090

**8 Registration Number(s)**

41/21.2/0487

**9 Date of first authorization / renewal of the authorization**

Date of Registration of medicine: 04 June 2010

**10 Date of revision of text**

15 May 2022