SCHEDULING STATUS: S3

PROPRIETARY NAME AND DOSAGE FORM:

GALVUS 50 mg tablet

COMPOSITION:

GALVUS 50 mg: Each tablet contains 50 mg vildagliptin

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

Contains sugar (lactose)

PHARMACOLOGICAL CLASSIFICATION:

A 21.2. Oral hypoglycaemics

PHARMACOLOGICAL ACTION:

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.

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 (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 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 [^{14}C] - 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 Contraindications).

Renal impairment:

In subjects with mild, moderate, and severe renal impairment, and end - stage renal disease (ESRD) patients on haemodialysis, systemic exposure to vildagliptin was increased (C_{max} 8 % - 66 %; AUC 32 % - 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. The elimination half-life of vildagliptin was not affected by renal impairment. (See Contraindications and Dosage and directions for use).

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.

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.

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.

WARNINGS AND SPECIAL PRECAUTIONS:

Hepatic impairment:

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

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:

Vildagliptin is not recommended in patients with New York Heart Association (NYHA) Class III. Rates of reported cardiac adverse events were higher in patients with NYHA functional class III treated with vildagliptin than with placebo.

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.

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.

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.

Effects on ability to drive and use machines:

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

INTERACTIONS:

GALVUS has a low potential for interactions. Since GALVUS 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, GALVUS 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.

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.

DOSAGE AND DIRECTIONS FOR USE:

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 Pharmacokinetic properties: special populations).

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 also Pharmacokinetic properties: 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 Pharmacokinetic properties: Special populations).

SIDE 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)

Nervous system disorders	
Common:	*Tremor, *dizziness, headache; ***chills
****General disorders and administration site conditions**	
Common:	Asthenia, peripheral oedema
*****Gastrointestinal disorders**	
Common:	Nausea, gastroesophageal reflux disease, constipation
Uncommon:	Diarrhoea, flatulence
Metabolism and nutritional disorders	
Common:	*** Decreased blood glucose; **** 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 Warnings and Special Precautions)
- Urticaria, pancreatitis
- Localised exfoliation or blisters
- Arthralgia, sometimes severe

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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.

IDENTIFICATION:

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

PRESENTATION:

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.

STORAGE INSTRUCTIONS:

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.

REGISTRATION NUMBER:

41/21.2/0487

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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