AUSTRALIAN PRODUCT INFORMATION – GALVUS® (VILDAGLIPTIN) TABLETS

1 NAME OF THE MEDICINE

The active ingredient of GALVUS is vildagliptin.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Vildagliptin is a white to slightly yellowish or slightly greyish crystalline powder with a melting point/range of approximately 150°C. It is freely soluble in water.

Each GALVUS tablet contains 50 mg vildagliptin, lactose anhydrous, magnesium stearate, cellulose – microcrystalline and sodium starch glycollate.

Excipients with known effect: lactose

3 PHARMACEUTICAL FORM

GALVUS (vildagliptin) is available as a 50 mg tablet.

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of diabetes mellitus type 2 in persons 18 years of age and older, as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes:

- As monotherapy, in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance.
- In dual combination with one of metformin, a sulfonylurea or pioglitazone when diet, exercise and the single agent do not result in adequate glycaemic control.
- In triple combination with a sulfonylurea and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control.
- In combination with insulin (with or without metformin) when diet, exercise and a stable dose of insulin do not result in adequate glycaemic control.

4.2 DOSE AND METHOD OF ADMINISTRATION

The management of antidiabetic therapy should be individualised.

Doses greater than 100 mg are not recommended.

Vildagliptin can be administered orally with or without a meal.

The 50 mg dose should be administered once daily in the morning. The 100 mg daily dose should be administered as two divided doses of 50 mg taken in the morning and evening.

If a dose of Galvus is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.

As monotherapy

The recommended dose of Galvus is 50 mg twice daily (100 mg daily dose) for monotherapy.

In dual combination therapy

When used in dual combination with metformin or a thiazolidinedione (clinical experience is with pioglitazone as dual therapy), the recommended dose of vildagliptin is 50 mg once daily or 100 mg (50 mg twice) daily.

When used in dual combination with a sulfonylurea (clinical experience is with glimepiride as dual therapy), 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 and was associated with a higher rate of hypoglycaemia than the 50 mg dose.

In combination with insulin

The recommended dose of Galvus is 50 mg once daily or 100 mg (50 mg twice) daily in combination with insulin (with or without metformin).

In triple combination therapy

The recommended dose of Galvus is 100mg daily (50 mg twice a day) for triple combination with metformin and a sulfonylurea.

Patients with hepatic impairment

Vildagliptin is not recommended in patients with hepatic impairment including patients with a pre-treatment ALT or AST > 2.5x the ULN.

Patients with renal impairment

Glomerular Filtration Rate (GFR) is to be estimated prior to commencement of therapy.

No dosage adjustment of vildagliptin is required in patients with mild chronic kidney disease (eGFR 60-89 mL/min/1.73m2). In patients with moderate (eGFR 30-59 mL/min/1.73m2) or severe (eGFR 15-29 mL/min/1.73m2) renal impairment or End Stage Renal Disease (ESRD), the recommended dose of vildagliptin is 50 mg once daily (see Section 4.4 Special warnings and precautions for use-Use in renal impairment, Section 5.1 Pharmacodynamic properties, Clinical trials and Section 5.2 Pharmacokinetic properties, Special populations).

Elderly patients

In patients ≥ 65 years of age and ≥ 75 years of age treated with vildagliptin, no differences were observed in the overall safety, tolerability, or efficacy between this elderly population and younger patients. However, renal function typically declines in elderly patients which increases overall exposure and peak plasma concentration of vildagliptin. No dosage adjustments are necessary in the elderly patients with mild renal impairment. For elderly patients with moderate or severe renal impairment, or End Stage Renal Disease, similar dosing adjustment should be followed as for younger patients (See Section 5.2 Pharmacokinetic properties, Special Populations, and Section 4.2 Dose and method of administration, Patients with renal impairment).

Paediatric patients

Vildagliptin has not been studied in patients under 18 years of age; therefore, the use of vildagliptin in paediatric patients is not recommended (see Section 5.2 Pharmacokinetic properties, Special Populations).

4.3 CONTRAINDICATIONS

Hypersensitivity to vildagliptin or to any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Cardiac failure

A clinical trial of vildagliptin in patients with NYHA functional class I-III showed that treatment with vildagliptin was not associated with a change in left-ventricular function or worsening of pre-existing CHF versus placebo. Clinical experience in patients with NYHA functional class III treated with vildagliptin is still limited and the results are inconclusive (see Section 5.1 Pharmacodynamic properties, Clinical Trials).

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.

Acute pancreatitis

Use of vildagliptin has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptoms of acute pancreatitis.

If pancreatitis is suspected, vildagliptin should be discontinued; if acute pancreatitis is confirmed, vildagliptin should not be restarted. Caution should be exercised in patients with a history of acute pancreatitis.

Other

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

Use in hepatic impairment

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

<u>Liver enzyme monitoring:</u>

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 vildagliptin. LFTs should be monitored during vildagliptin 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 ULN or

greater persist, withdrawal of therapy with vildagliptin is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue vildagliptin and contact their physician immediately. Following withdrawal of treatment with vildagliptin and LFT normalisation, vildagliptin should not be reinitiated.

Use in renal impairment

There is limited experience in patients with End Stage Renal Disease (ESRD) on haemodialysis. Therefore, Galvus should be used cautiously in these patients.

Use in the elderly

Of the 2900 patients treated with vildagliptin, 543 (18.9%) were ≥65 years of age and 109 (3.8%) were ≥75 years of age. There were no differences observed in overall safety, tolerability, or efficacy between these patients and younger patients.

Paediatric use

The safety and effectiveness of vildagliptin in paediatric patients have not been established.

Effects on Laboratory tests

See Section 4.4 Special Warnings and Precautions for Use – Use in Hepatic Impairment, and Liver enzyme monitoring.

Arthralgia

There have been post-marketing reports of joint pain, which may be severe, in patients taking DPP-4 inhibitors. Onset of symptoms following initiation of treatment may be rapid or may occur after longer periods. Discontinuation of therapy should be considered in patients who present with or experience an exacerbation of joint symptoms during treatment with DPP-4 inhibitors.

Bullous pemphigoid

Post-marketing cases of bullous pemphigoid requiring hospitalisation have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving Galvus. If bullous pemphigoid is suspected, Galvus should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Vildagliptin has low potential for drug interaction. Since vildagliptin is not a cytochrome (CYP) P450 enzyme substrate and does not inhibit or induce CYP P450 enzymes, it is not likely to interact with the concomitant medications that are substrates, inhibitors or inducers of these enzymes.

Furthermore, vildagliptin is not likely to interact with the concomitant medications that are substrates, inhibitors or inducers of CYP P450 enzymes nor does it affect metabolic clearance of co-medications metabolised by CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5. Drug-drug interaction studies were conducted with the following commonly co-

prescribed medications for patients with type 2 diabetes or medications with a narrow therapeutic window.

Glibenclamide

Coadministration of vildagliptin (100 mg twice daily) with glibenclamide (10 mg once daily) had no significant effect on the steady-state pharmacokinetics of vildagliptin. Vildagliptin did not alter the steady-state pharmacokinetics of glibenclamide.

Pioglitazone

Coadministration of vildagliptin (100 mg once daily) with pioglitazone (45 mg once daily) did not alter the steady-state pharmacokinetics of vildagliptin. Vildagliptin had no effect on the steady-state pharmacokinetics of pioglitazone measured by the parent pioglitazone and its two active metabolites, MIII and MIV.

Metformin

Coadministration of vildagliptin (100 mg once daily) with metformin (1000 mg once daily) did not alter the steady-state pharmacokinetics of metformin. Metformin (1000 mg once daily) did not affect total exposure to vildagliptin at steady state. The Cmax of vildagliptin was decreased by 18%, which is not considered to be clinically relevant.

Amlodipine

Coadministration of vildagliptin (100 mg once daily) with amlodipine (5 mg once daily) given in combination to healthy subjects, did not alter the steady-state pharmacokinetics of amlodipine (5 mg once daily). Similarly, the steady-state pharmacokinetics of vildagliptin were unaffected by coadministration of amlodipine.

Valsartan

Coadministration of vildagliptin (100 mg once daily) with valsartan (320 mg once daily) did not alter the steady-state pharmacokinetics of vildagliptin. Coadministration of vildagliptin with valsartan resulted in an increased exposure to valsartan (AUC by 24% and Cmax by 14%). However, these changes are not considered to be clinically relevant.

Ramipril

Coadministration of vildagliptin (100 mg once daily) with ramipril (5 mg once daily) to healthy subjects, did not alter the steady-state pharmacokinetics of ramipril and its active metabolite, ramiprilat. Similarly, ramipril did not affect the steady-state pharmacokinetics of vildagliptin.

Simvastatin

Coadministration of vildagliptin (100 mg once daily) with simvastatin (80 mg once daily) did not alter the steady-state pharmacokinetics of simvastatin and its active metabolite, simvastatin hydroxyacid. Similarly, simvastatin did not influence the steady-state pharmacokinetics of vildagliptin.

Digoxin

Coadministration of vildagliptin (100 mg once daily) with digoxin (0.5 mg loading dose on Day 1 and a 0.25 mg maintenance dose from Day 2 to Day 7) did not affect the pharmacokinetics of digoxin at steady state, and digoxin did not alter the pharmacokinetics of vildagliptin.

Warfarin

Coadministration of vildagliptin (100 mg once daily) with warfarin (25 mg single dose) did not alter the pharmacokinetics of warfarin and warfarin did not influence the pharmacokinetics of vildagliptin (100 mg once daily). Coadministration of vildagliptin did not affect the pharmacodynamic parameters of prothrombin times such as AUC_{PT}, PT_{max}, AUC_{INR}, INR_{max} following administration of warfarin 25 mg in comparison with coadministration of placebo.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No studies on the effect on human fertility have been conducted for Galvus. Vildagliptin did not impair male or female fertility or early embryonic development in rats at oral doses corresponding to 160 times human exposure at the maximum clinical dose.

Use in pregnancy – Pregnancy Category B3

Vildagliptin was not teratogenic in either rats or rabbits at exposures up to ca 115 times and 40 times the maximum expected human exposure, respectively. A slight treatment-related increase in the incidence of fetal rib abnormalities was observed in the fetuses of rats at oral doses of 225 mg/kg/day (approximately 30 times the human AUC exposure at the 100 mg dose). There is insufficient experience with Galvus in pregnant women. Vildagliptin should not be used during pregnancy unless the benefit to the mother outweighs the potential risk to the foetus. Attainment of strict normoglycaemia during pregnancy may require conversion to insulin monotherapy.

Use in lactation

Vildagliptin is excreted in the milk of lactating rats. As it is not known whether vildagliptin is excreted in human milk, vildagliptin should not be administered to breastfeeding mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

The safety and tolerability of vildagliptin (50 mg qd, 50 mg bid and 100 mg qd) have been assessed by pooling data from more than 11,500 patients from 38 Phase II and III studies (including 3 open label studies) ranging in duration from 12 to more than 104 weeks. The studies used in this pooled analysis have assessed vildagliptin as monotherapy, add-on therapy to other oral anti-diabetic agents (metformin, TZD, SU and insulin) and as an initial combination therapy with metformin or pioglitazone. Patients not receiving vildagliptin (all comparators group) were taking only placebo or metformin, TZD, SU, acarbose or insulin. For the calculation of frequency of adverse drug reactions for the individual indications, safety data from a subset

of pivotal controlled trials of at least 12 week's duration was considered. Safety data were obtained from 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) who received vildagliptin as monotherapy or in combination with another agent.

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, gender, 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. 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 vildagliptin in double blind studies as monotherapy and add-on therapy are listed below, for each indication, by MedDRA system organ class and absolute frequency. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Monotherapy

The overall incidence of withdrawal 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 50mg 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 1373) of patients treated with vildagliptin 50mg 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.

Vildagliptin is weight neutral when administered as monotherapy.

Table 1 Adverse reactions reported in patients who received vildagliptin 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
General disorders and administration site conditions	
Uncommon	Oedema peripheral

Long-term clinical trials of up to 2 years did not show any additional safety signals or unforeseen risks with vildagliptin monotherapy.

Combination with metformin

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

Vildagliptin is weight neutral when administered in combination with metformin.

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

Nervous system disorders	
Common	Headache, tremor, dizziness

Long term clinical trials of up to more than 2 years did not show any additional safety signal or unforeseen risks when vildagliptin was added on to metformin.

Combination with glimepiride

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

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

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

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

Nervous system disorders	
Common	Tremor, headache, dizziness
General disorders and administration site conditions	
Common	Asthenia

Combination with pioglitazone

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

In clinical trials, no hypoglycaemia events were reported in patients receiving vildagliptin 50 mg once daily plus pioglitazone 45 mg, hypoglycaemia was uncommon in patients receiving vildagliptin 50 mg twice daily plus pioglitazone 45 mg (0.6%) but common in patients receiving placebo plus 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 vildagliptin 50 mg daily and vildagliptin 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 vildagliptin 50 mg once daily (n= 290) or 50mg twice daily (n=158) daily in combination with a thiazolidinedione in double-blind studies

Investigations	
Common	Weight increase
General disorders and administration site conditions	
Common	Oedema peripheral

Combination with insulin

Pooled safety data from two controlled clinical trials using vildagliptin 50 mg twice daily in combination with insulin, with or without concomitant metformin, identified the following adverse reactions:

Common: Headache, nausea, gastrooesophageal reflux disease, chills, blood glucose decreased

Uncommon: Diarrhoea, flatulence

The overall incidence of withdrawal due to adverse reactions was 0.3% in the vildagliptin treatment group and there were no cases of withdrawal in the placebo group.

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

At the end of the study, the effect on mean body weight was neutral (+ 0.6 kg change from baseline in the vildagliptin group and no weight change in the placebo group).

The adverse effect profiles for the vildagliptin and placebo groups from the 24-week study investigating vildagliptin as add-on to insulin treatment (with or without metformin) is shown in Table 5.

Table 5 Adverse effects reported in patients who received vildagliptin 50 mg twice daily vs placebo in combination with insulin (with or without metformin)

	Vildagliptin N=227 (n, %)	**Placebo** N=221 (n, %)
Adverse effects reported (AE)	131 (57.7%)	105 (47.5%)
Serious adverse effects (SAE)	9 (4.0%)	9 (4.1%)
Discontinuation due to AEs	9 (4.0%)	5 (2.3%)
Deaths	0 (0.0%)	1 (0.5%)
Hypoglycaemia	19 (8.4%)	16 (7.2%)

Combination with metformin and a sulfonylurea

There were no cases of withdrawal reported due to adverse reactions in the vildagliptin + metformin + glimepiride treatment group vs 0.6% in the placebo + metformin + glimepiride treatment group.

The incidence of hypoglycaemia was common (≥1/100, <1/10) in both treatment groups, but was numerically greater for the vildagliptin + metformin + glimepiride group (5.1%) than the placebo + metformin + glimepiride group (1.9%). One severe hypoglycaemic event was reported in the vildagliptin group.

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

Table 6 Adverse reactions reported in patients who received vildagliptin 50 mg twice daily in combination with metformin and sulfonylurea

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

Special populations:

The adverse effect profiles for the vildagliptin and placebo groups from the 24-week core study and the 28-week extension study in patients with type 2 diabetes and moderate or severe renal insufficiency are shown in Table 7 and Table 8.

Table 7 Adverse effects reported in patients with moderate renal insufficiency who received vildagliptin 50 mg once daily vs. placebo after 24 weeks or 52 weeks of treatment

Moderate renal insufficiency	24 weeks of treatment		52 weeks of treatment	
	Vildagliptin N = 163 n (%)	Placebo N = 129 n (%)	Vildagliptin N = 122 n (%)	Placebo N = 89 n (%)
AEs	110 (67.5%)	94 (72.9%)	103 (84.4%)	76 (85.4%)

Moderate renal insufficiency	24 weeks of treatment		52 weeks of treatment	
	Vildagliptin	Placebo	Vildagliptin	Placebo
SAEs	15 (9.2%)	11 (8.5%)	26 (21.3%)	17 (19.1%)
Discontinued due to AEs	4 (2.5%)	7 (5.4%)	6 (4.9%)	5 (5.6%)
Deaths	1 (0.6%)	1 (0.8%)	1 (0.8%)	1 (0.0%)
Hypoglycaemia	28 (17.2%)	15 (11.6%)	32 (26.2%)	15 (16.9%)

Table 8 Adverse effects reported in patients with severe renal insufficiency who received vildagliptin 50 mg once daily vs. placebo after 24 weeks or 52 weeks of treatment

Severe renal insufficiency	24 weeks of treatment		52 weeks of treatment	
	Vildagliptin N = 124 n (%)	Placebo N = 97 n (%)	Vildagliptin N = 94 n (%)	Placebo N = 64 n (%)
AEs	90 (72.6%)	72 (74.2%)	80 (85.1%)	56 (87.5%)
SAEs	23 (18.5%)	20 (20.6%)	23 (24.5%)	16 (25.0%)
Discontinued due to AEs	11 (8.9%)	6 (6.2%)	9 (9.6%)	4 (6.3%)
Deaths	3 (2.4%)	4 (4.1%)	3 (3.2%)	1 (1.6%)
Hypoglycaemia	19 (15.3%)	12 (12.4%)	17 (18.1%)	11 (17.2%)

The adverse effect profiles for the vildagliptin and sitagliptin groups of the 24-week core study and 28-week extension study investigating patients with type 2 diabetes and severe renal insufficiency are shown in Table 9.

Table 9 Adverse effects reported in patients with severe renal insufficiency who received vildagliptin 50 mg once daily vs. sitagliptin

Severe renal insufficiency	24 weeks of treatment		52 weeks of treatment	
	Vildagliptin N = 83 n (%)	Sitagliptin N = 65 n (%)	Vildagliptin N = 46 n (%)	Sitagliptin N = 38 n (%)

Severe renal insufficiency	24 weeks of treatment		52 weeks of treatment	
	Vildagliptin	Sitagliptin	Vildagliptin	Sitagliptin
AEs	68 (81.9%)	56 (86.2%)	44 (95.7%)	36 (94.7%)
SAEs	20 (24.1%)	15 (23.1%)	15 (32.6%)	10 (26.3%)
Discontinued due to AEs	6 (7.2%)	6 (9.2%)	6 (13.0%)	4 (10.5%)
Deaths	2 (2.4%)	2 (3.1%)	0 (0.0%)	0 (0.0%)
Hypoglycaemia	13 (15.7%)	10 (15.4%)	11 (23.9%)	7 (18.4%)

Post-marketing Experience – Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Galvus via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency, which is therefore categorized as not known.

- Hepatitis - reversible upon drug discontinuation (see Section 4.4 Special warnings and precautions for use).
- Urticaria, bullous and exfoliative skin lesions, including bullous pemphigoid (see Section 4.4 Special Warnings and Precautions for Use).
- Cutaneous vasculitis
- Pancreatitis.
- Arthralgia, sometimes severe
- Cholecystitis

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

In healthy subjects (seven to fourteen subjects per treatment group), GALVUS (vildagliptin) 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 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. 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 (twice the ULN). All adverse events and laboratory abnormalities resolved after study drug discontinuation.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group, ATC code

Drugs used in diabetes, dipeptidyl peptidase 4 (DPP-4) inhibitors, ATC code: A10BH02.

Mechanism of action

Vildagliptin, a member of the class that enhances islet cell insulin secretion via an augmented incretin effect, is a high affinity dipeptidyl-peptidase-4 (DPP-4) inhibitor that improves glycaemic control.

The administration of vildagliptin results in rapid and near-complete inhibition of DPP-4 activity. Vildagliptin shows weak inhibition of, and rapid dissociation from DPP-8 and DPP-9, compared to DPP-4. 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).

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 reduced glucagon secretion. There is a reduction in inappropriate glucagon release during meals. The increase in the insulin/glucagon ratio with hyperglycaemia, due to increased incretin hormone levels, may thus be expected to decrease 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 trials

More than 15,000 patients with type 2 diabetes participated in double-blind, placebo- or active-controlled clinical trials including some studies of more than 2 years of treatment duration. In these studies, vildagliptin was administered to more than 9,000 patients at daily doses of 50 mg once daily, 50 mg twice daily or 100 mg once daily. More than 5,000 male and more than 4,000 female patients received vildagliptin 50 mg once daily or 100 mg daily. More than 1,900 patients receiving vildagliptin 50 mg once daily or 100 mg daily were ≥ 65 years of age. In these trials, vildagliptin was administered as monotherapy in drug-naïve patients with type 2 diabetes or in combination in patients not adequately controlled by other antidiabetic medicinal products. Monotherapy studies suggested that vildagliptin on its own had slightly less efficacy compared to sulfonylureas or pioglitazone. The role of vildagliptin in dual therapy with

sulfonylureas and pioglitazone is incompletely defined. No morbidity or mortality data are available.

Overall, vildagliptin improved glycaemic control when given as monotherapy or when used in combination with metformin, a sulfonylurea, or a thiazolidinedione as measured by clinically relevant reductions in HbA_{1c} from baseline at the study endpoint (see **Table 10**). Long-term extension studies with vildagliptin as add-on therapy to metformin, glimepiride, or pioglitazone generally demonstrated continued glycaemic benefit at week 52. However, results were variable across studies. Therefore, the individual long-term response may vary.

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

Table 10 Key efficacy results of vildagliptin in placebo-controlled monotherapy and in combination therapy trials (primary efficacy ITT population)

	Primary endpoint (weeks)	**Mean baseline HbA_{1c} (%)**	**Mean change from baseline in HbA_{1c} (%)**	**Difference from placebo group (95%CI)**	**Patients achieving a ≥ 0.7% reduction in A1c (%)**
Monotherapy studies					
Vildagliptin 50 mg once daily (N=104) [Study 2301]	24	8.2	-0.8	-0.5** (-0.8, -0.1)	62 (60%)
Vildagliptin 50 mg twice daily (N=90) [Study 2301]	24	8.6	-0.8	-0.5** (-0.8, -0.1)	59 (66%)
Vildagliptin 50 mg once daily (N=84) [Study 2384]	24	8.3	-0.5	-0.5** (-0.9, -0.1)	37 (44%)
Vildagliptin 50 mg twice daily (N=79) [Study 2384]	24	8.4	-0.7	-0.7** (-1.1, -0.4)	43 (54%)
Combination studies					
Vildagliptin 50 mg once daily + metformin (N=143) [Study 2303]	24	8.4	-0.5	-0.7* (-1.0, -0.5)	66 (46%)

Vildagliptin 50 mg twice daily + metformin (N=143) [Study 2303]	24	8.4	-0.9	-1.1* (-1.4, -0.8)	86 (60%)
Vildagliptin 50 mg once daily + pioglitazone (N=124) [Study 2304]	24	8.6	-0.8	-0.5* (-0.7, -0.2)	67 (54%)
Vildagliptin 50 mg twice daily + pioglitazone (N=136) [Study 2304]	24	8.7	-1.0	-0.7* (-0.9, -0.4)	93 (68%)
Vildagliptin 50 mg once daily + glimepiride (N=132) [Study 2305]	24	8.5	-0.6	-0.6* (-0.9, -0.4)	63 (47%)
Vildagliptin 50 mg twice daily + metformin + glimepiride (N=152) [Study 23152]	24	8.8	-1.0	-0.8* (-1.0, -0.5)	96 (63%)
Vildagliptin 50 mg twice daily + insulin, with or without metformin (N=221) [Study 23135]	24	8.8	-0.8	-0.7* (-0.9, -0.5)	135 (61%)

* p< 0.05 for comparison versus placebo + background therapy
** p< 0.05 for comparison versus placebo

Monotherapy:

In a 52-week trial (Study 2309), vildagliptin (50 mg twice daily) reduced baseline HbA1c by -1% compared to -1.4% for metformin (titrated to 2 g/day). Patients treated with vildagliptin reported significantly lower incidences of gastrointestinal adverse reactions versus those treated with metformin.

In a 24-week trial (Study 2327), vildagliptin (50 mg twice daily) 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 HbA1c 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).

In a long-term trial of 2 years (Study 2310), vildagliptin (50 mg twice daily) was compared to gliclazide (up to 320 mg/day). After two years, mean reduction in HbA1c was -0.5% for vildagliptin and -0.6% for gliclazide. Vildagliptin had less of a weight gain (0.75 kg) and fewer hypoglycaemic events (0.7%) than gliclazide (1.6 kg and 1.7%, respectively).

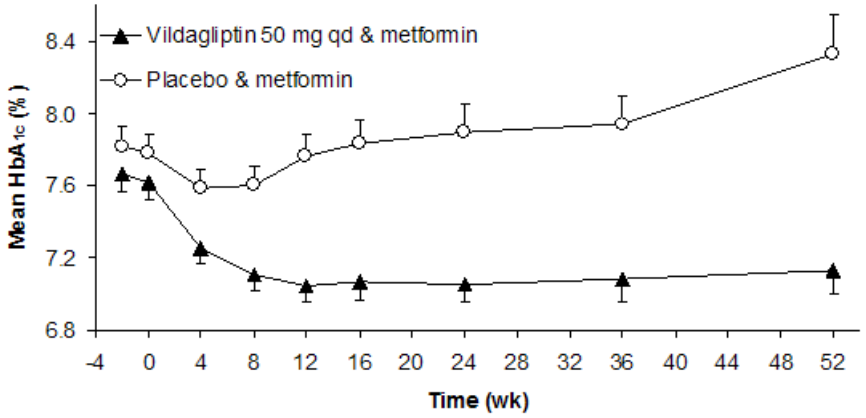
Combination with Metformin:

In a double-blind, placebo-controlled 24 week trial (Study 2303; n=544) in patients with type 2 diabetes whose hyperglycaemia was inadequately controlled on a maximal dose of metformin alone (mean metformin dose at baseline = 2100 mg/day), the addition of vildagliptin (50 mg once daily or 100 mg daily, as a divided dose of 50 mg in the morning and 50 mg in the evening) to metformin for 24 weeks led to statistically significant reductions in HbA_{1c} and increased the proportion of patients achieving at least a 0.7% reduction in HbA_{1c} when compared to patients who were continued on metformin plus placebo. Group mean baseline HbA_{1c} ranged from 8.3% (placebo plus metformin) to 8.4% (in both vildagliptin plus metformin groups) (see **Table 10**). Vildagliptin combined with metformin resulted in additional statistically significant mean reductions in HbA_{1c} compared to placebo (between group differences of -0.7% to -1.1% for vildagliptin 50 mg and 100 mg, respectively). The proportion of patients who achieved a decrease of ≥0.7% in HbA_{1c} from baseline was statistically significantly higher in both vildagliptin plus metformin groups (46% and 60%, respectively) versus the metformin plus placebo group (20%). Patients on the combination of vildagliptin plus metformin did not experience a meaningful change in body weight compared to baseline. The incidence of gastrointestinal side effects ranged from 10% to 15% in the vildagliptin plus metformin groups as compared to 18% in the metformin plus placebo group. Vildagliptin added to metformin significantly reduced FPG compared to metformin plus placebo (-0.8 mmol/L for 50 mg once daily, and -1.7 mmol/L for 50 mg twice daily).

The effect of vildagliptin in combination with metformin was evaluated in another, double-blind, placebo-controlled add-on clinical trial (Study 2204E1) of 52 weeks total duration (12-week core study plus a 40-week extension) involving 132 patients with type 2 diabetes on stable doses of metformin (1500 mg-3000 mg daily). The addition of vildagliptin (50 mg once daily) to metformin resulted in an additional statistically significant reduction in mean HbA_{1c} (between group difference of -0.6%) from baseline compared to placebo plus metformin (+0.1%) at the end of the 12-week study interval (mean baseline HbA_{1c} of 7.7% and 7.9%, respectively). Of these patients, 71 continued add-on treatment with vildagliptin or placebo for an additional 40 weeks (placebo-controlled, double-blind extension). At 52 weeks, mean change from baseline in HbA_{1c} was statistically significantly greater and sustained with vildagliptin (50 mg) plus metformin versus patients continued on metformin plus placebo (between group difference of -1.1%).

These data indicate vildagliptin plus metformin provides a durable effect on glycaemic control over 52 weeks (See **Figure 1**). In contrast, glycaemic control in the metformin plus placebo group deteriorated over the course of the study.

Figure 1. Mean HbA_{1c} Over Time in a 52-Week Study (12-Week Core Study and 40-Week Extension) Comparing Vildagliptin Plus Metformin to Placebo Plus Metformin in Patients Inadequately Controlled with Metformin



In a double-blind, active-controlled 24 week trial (Study 2354; n=576), vildagliptin (100 mg/day; 50 mg in the morning and 50 mg in the evening) was compared to pioglitazone (30 mg once daily) in patients with type 2 diabetes inadequately controlled with metformin alone. Mean reductions from baseline HbA_{1c} of 8.4% were - 0.9% with vildagliptin added to metformin and -1.0% with pioglitazone added to metformin. The decrease in HbA_{1c} from baseline >9.0% was greater (-1.5%) in both treatment groups. Patients receiving pioglitazone in addition to metformin experienced an increase in weight of 1.9 kg while those receiving vildagliptin in addition to metformin experienced an increase in weight of 0.3 kg.
In a 28 week extension, HbA_{1c} reductions were similar between treatment groups and the difference in body weight further increased.

In a long term, double-blind, active-controlled trial of up to more than 2 years (Study 2308; n=3118), vildagliptin (100 mg/day; 50 mg in the morning and 50 mg in the evening) was compared to glimepiride (up to 6 mg/day) in patients with type 2 diabetes treated with metformin. After one-year, mean reductions in HbA_{1c} were -0.4% with vildagliptin added to metformin and -0.5% with glimepiride added to metformin. Body weight change with vildagliptin was -0.2 kg vs + 1.6 kg with glimepiride. The incidence of hypoglycaemia was significantly lower in the vildagliptin group (1.7%) than in the glimepiride group (16.2%). At study endpoint (2 years), the HbA_{1c} was similar to baseline values in both treatment groups and the body weight changes and the differences in hypoglycaemia were maintained.

Combination with Glimepiride:

The benefit of vildagliptin as add-on therapy was investigated in a double-blind, placebo-controlled add-on trial (Study 2305; n=515), in patients with type 2 diabetes whose hyperglycaemia was inadequately controlled after switching from half maximal recommended doses of a sulfonylurea to glimepiride (4 mg). The addition of vildagliptin (50 mg once daily or 100 mg daily, as a divided dose of 50 mg in the morning and 50 mg in the evening) for 24 weeks led to additional statistically significant reductions in HbA_{1c} from baseline versus patients continued on glimepiride plus placebo. The difference from placebo plus glimepiride was -0.64 in the 50 mg once daily group and -0.70% in the 50 mg twice daily group. Patients receiving vildagliptin in combination with glimepiride experienced either no increase in body weight

(with vildagliptin 50 mg daily) or a slight increase (with vildagliptin 100 mg daily) relative to baseline values. Vildagliptin added to glimepiride reduced FPG compared to placebo plus glimepiride (-0.5 mmol/L for 50 mg once daily, and -0.6 mmol/L for 100 mg once daily, as divided dose of 50 mg in the morning and 50 mg in the evening).

Combination with Pioglitazone:

In a double-blind, placebo-controlled add-on trial (Study 2304; n=463) in patients with type 2 diabetes whose hyperglycaemia was inadequately controlled with prior thiazolidinedione monotherapy, patients were randomized to either continued thiazolidinedione monotherapy (pioglitazone 45 mg once daily plus placebo) or to the combination of the thiazolidinedione (pioglitazone 45 mg) plus vildagliptin (either 50 mg once daily or 50 mg twice daily) for 24 weeks. Group mean baseline HbA_{1c} ranged from 8.6% (vildagliptin 50 mg daily plus pioglitazone) to 8.7% (vildagliptin 50 mg twice daily plus pioglitazone, or placebo plus pioglitazone).

The addition of vildagliptin led to statistically significant reductions in HbA_{1c} and increased the proportion of patients achieving at least a 0.7% reduction in HbA_{1c} when compared to patients who were continued on the thiazolidinedione alone. Vildagliptin combined with pioglitazone resulted in additional statistically significant mean reductions in HbA_{1c} compared to pioglitazone plus placebo (between group differences of -0.5% to -0.7% for vildagliptin 50 mg once daily and twice daily, respectively). The proportion of patients who achieved a decrease of ≥0.7% in HbA_{1c}, from baseline was statistically significantly higher in both vildagliptin plus pioglitazone groups (54% and 68%, respectively) versus the pioglitazone plus placebo group (38%). Patients on the combination experienced either no increase in body weight (those receiving vildagliptin 50 mg daily plus pioglitazone) or a slight increase (those receiving vildagliptin 50 mg twice daily plus pioglitazone) relative to pioglitazone plus placebo.

Vildagliptin added to pioglitazone reduced FPG compared to placebo plus pioglitazone (-0.3 mmol/L for 50 mg vildagliptin once daily, and -0.7 mmol/L for 100 mg vildagliptin once daily, as divided dose of 50 mg in the morning and 50 mg in the evening).

Combination with Insulin:

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 (N = 276) or without (N = 173) concomitant metformin. Vildagliptin in combination with insulin significantly decreased HbA1c compared with placebo: in the overall population, the placebo-adjusted mean reduction from mean baseline HbA1c of 8.8% was -0.72%. In the subgroups treated with insulin with or without concomitant metformin the placebo-adjusted mean reduction in HbA1c was -0.63% and -0.84%, respectively. The incidence of hypoglycaemia in the overall population was 8.4% and 7.2% in the vildagliptin and placebo groups, respectively. Changes in mean body weight were +0.2 kg and -0.7kg in the vildagliptin and placebo groups, respectively.

Combination with Metformin and Glimepiride:

A 24-week randomized, double-blind, placebo-controlled study was conducted in 318 patients to evaluate the efficacy and safety of vildagliptin (50 mg twice daily) in combination with metformin (≥ 1,500 mg daily) and glimepiride (≥ 4 mg daily). Vildagliptin in combination with

metformin and glimepiride significantly decreased HbA1c compared with placebo: the placebo-adjusted mean reduction from mean baseline HbA1c 8.8% was -0.76%.

Special populations:

In a 24-week, double-blind placebo-controlled trial, vildagliptin (50 mg once daily) reduced HbA1c by -0.74% from a mean baseline of 7.9% in patients with moderate renal impairment and -0.88% from a mean baseline of 7.7% in patients with severe renal impairment. Reductions in patients with moderate and severe renal impairment in the placebo group were -0.21% and -0.32% respectively. The difference to placebo was statistically significant in both patient groups. In this study, 68.4% of patients with moderate renal impairment and 80.5% of patients with severe renal impairment were on background insulin therapy. At 52 weeks of treatment in the extension study, vildagliptin (50 mg once daily) reduced HbA1c by -0.57% from a mean baseline of 7.8% in patients with moderate renal impairment and -0.81% from a baseline of 7.7% in patients with severe renal impairment. Reductions in patients with moderate and severe renal impairment in the placebo group were -0.14% and -0.08% respectively. The difference to placebo was statistically significant in both patient groups.

In a 24-week double-blind study comparing vildagliptin 50 mg qd to sitagliptin 25 mg qd in patients with severe renal impairment, vildagliptin reduced HbA1c by -0.54% from a mean baseline of 7.5%, while sitagliptin reduced HbA1c by -0.56% from a slightly higher baseline of 7.8%. 81.8% of patients in this study were on background insulin therapy. At 52 weeks of treatment in the extension study, the mean changes in HbA1c from baseline were also similar between the two treatments: -0.49% in the vildagliptin group (baseline 7.5%) and -0.53% in the sitagliptin group (baseline 7.8%).

A 52-week multi-centre, randomized, double-blind trial was conducted in patients with type 2 diabetes and congestive heart failure (CHF) New York Heart Association (NYHA) functional class I - III to evaluate the effect of vildagliptin 50 mg bid (N=128) compared to placebo (N=126) on left ventricular ejection fraction (LVEF). Vildagliptin was not associated with a change in left-ventricular function or worsening of pre-existing CHF. Adjudicated cardiovascular events were overall balanced. There were more cardiac events in vildagliptin-treated patients with NYHA class III heart failure compared to placebo. However there were imbalances in baseline CV risk favouring placebo and the number of events was low, precluding firm conclusions. Vildagliptin significantly decreased HbA1c compared with placebo (difference of 0.6%) from a mean baseline of 7.8%. In the subgroup of patients with NYHA class III heart failure, the decrease in HbA1c compared to placebo was lower (difference 0.3%) but this conclusion is limited by the small number of patients (n=44). The incidence of hypoglycaemia in the overall population was 4.7% and 5.6% in the vildagliptin and placebo groups, respectively.

In a 24-week double-blind placebo-controlled trial in elderly patients ≥ 70 years, vildagliptin (50 mg once or twice daily) reduced HbA1c by -0.86% from mean baseline of 7.9% and the difference to placebo of -0.57% was statistically significant. The proportion of patients reaching the investigator-defined HbA1c target at study end was higher for the vildagliptin group compared to the placebo group (52.6 % vs. 27.0%, respectively) and the difference was statistically significant. The proportion of patients who experienced hypoglycaemic events was low (2.2% in the vildagliptin and 0.7% in the placebo groups), and no patients experienced severe hypoglycaemia. Vildagliptin was safe and well tolerated in the elderly patients with an overall safety profile similar to placebo.

Cardiovascular risk

A meta-analysis of independently and prospectively adjudicated cardiovascular events from 37 phase III and phase IV monotherapy and combination therapy clinical studies of up to more than 2 years duration was performed. It involved 9,599 patients with type 2 diabetes treated with vildagliptin 50 mg once daily or 50 mg twice daily and showed that vildagliptin treatment was not associated with an increase in cardiovascular risk. The composite endpoint of adjudicated major adverse cardio-vascular events (MACE) including acute myocardial infarction, stroke or CV death was similar for vildagliptin versus combined active and placebo comparators [risk ratio (RR) 0.82 (95% confidence interval 0.61-1.11)] supporting the cardiovascular safety of vildagliptin. A MACE occurred in 83 out of 9,599 (0.86%) vildagliptin-treated patients and in 85 out of 7,102 (1.20%) comparator treated patients. Assessment of each individual MACE component showed no increased risk (similar RR). Confirmed heart failure events defined as heart failure requiring hospitalization or new onset of heart failure were reported in 41 (0.43%) vildagliptin-treated patients and 32 (0.45%) comparator-treated patients, with RR 1.08 (95% CI 0.68-1.70) showing no increased risk of heart failure in vildagliptin treated patients.

Fasting Plasma Glucose:

When administered as monotherapy and add-on therapy, vildagliptin produced clinically relevant and consistent mean reductions from baseline in fasting plasma glucose (FPG) concentrations.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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.

Following oral administration in the fasting state, vildagliptin is rapidly 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 litres, 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

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 unchanged vildagliptin accounts for 23% of the dose after oral administration. After intravenous administration to healthy subjects, the total plasma and renal clearances of vildagliptin are 41 litres/hour and 13 litres/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 the dose.

Special Populations

Geriatric patients:

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 to 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.

Gender:

No 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.

Paediatric patients:

No pharmacokinetic data available.

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 (ULN).

Renal impairment:

The AUC of vildagliptin 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. The 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 to- 3-fold higher than in patients with severe renal impairment. Dosage adjustment may be required in patients with renal impairment (see Section 4.2 Dose and method of administration).

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

Race:

There is no evidence that race affects the pharmacokinetics of vildagliptin.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Vildagliptin was not mutagenic in a bacterial reverse mutation assay and a human lymphocyte chromosomal aberration assay. Some clastogenic potential was exhibited in an in vitro micronucleus test in V79 Chinese hamster cells after long exposure to high, cytotoxic concentrations. However, no clastogenicity was observed in either mouse or rat micronucleus tests in vivo at up to ca 400 times the maximum human exposure, based on AUC. Furthermore, an in vivo mouse liver comet assay using the same dose was also negative. The weight of evidence indicates vildagliptin is unlikely to be genotoxic in humans at clinically relevant doses.

Carcinogenicity

Long-term oral studies with vildagliptin in rats and mice showed evidence of haemangiosarcomas at high exposures. Tumour incidence was increased at exposure levels 46-235 times (mice) and 150 times (rats) human exposure at the maximum clinical dose, based on AUC. No significant increase in incidence was observed at 15 to 80 (females) times human exposure in mice. No effect levels of ca 80 to 160 times human exposure were established in rats.

Mammary tumour incidence was increased in female mice at approximately 185 times the maximum anticipated human exposure to vildagliptin, but was not increased at ca 80 times. The tumours are thought to result from species-specific hormonal disturbances.

Based on the available data vildagliptin is not anticipated to present a carcinogenic risk at clinically relevant exposures.

Effects on skin

In a 13-week toxicology study in cynomolgus monkeys, skin lesions have been recorded at all oral doses administered (5 to 160 mg/kg/day). These were consistently located on the extremities (hands, feet, ears, scrotum and tail), and included flaking skin, peeling skin, scabs, tail sores and blisters. At 5 mg/kg/day (approximately equivalent to human AUC exposure at the 100 mg dose), lesions were reversible despite continued treatment. Necrotic lesions of the

tail were observed at ≥ 80 mg/kg/day (18 times human AUC exposure at the maximum recommended clinical dose). Skin lesions were not reversible in monkeys treated at 160 mg/kg/day (35 times human AUC exposure) during a 4-week recovery period. Skin lesions have not been observed in other animal species and no excess of skin lesions with vildagliptin treatment relative to comparator treatments have been observed in the human clinical trials programme.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 - Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

GALVUS is available in blisters packs containing 14, 60 or 112 tablets.

*Not all pack sizes may be marketed.

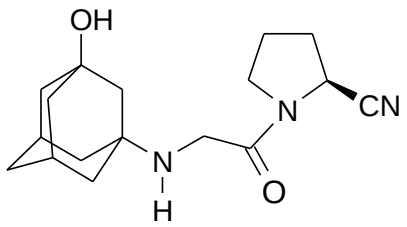
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

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

Chemical structure



Molecular formula: $C_{17}H_{25}N_3O_2$

Molecular weight: 303.40

CAS number

274901-16-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

02 March 2010

10 DATE OF REVISION

15 November 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.8	CDS v4.2 22 August 2023 revisions: addition of cholecystitis in Section 4.8 Post-marketing Experience – Adverse drug reactions from spontaneous reports and literature cases (frequency not known)