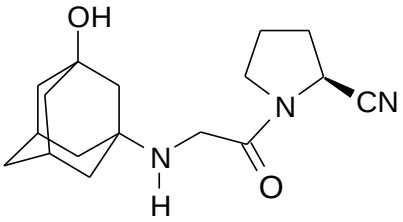
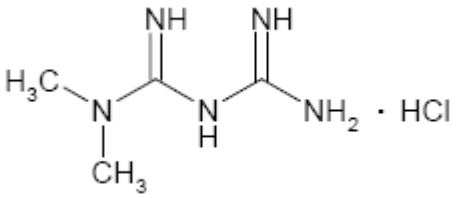
GALVUMET®
(vildagliptin/metformin hydrochloride)

NAME OF THE MEDICINE

Active ingredients:	Vildagliptin	Metformin hydrochloride
Chemical names:	(S)-1-[2-(3-Hydroxy-adamantan-1-ylamino)acetyl]-pyrrolidine-2(S)-carbonitrile	Imidodicarbinimidic, N,N-dimethyl-, monohydrochloride
Molecular formula:	C17H25N3O2	C4H11N5.HCl
Molecular weight:	303.40	165.6
Structural formula:		
CAS number:	274901-16-5	1115-70-4

DESCRIPTION

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

Metformin is a white crystalline powder which is almost odourless and hygroscopic. It is freely soluble in water, slightly soluble in ethanol (96%), and practically insoluble in chloroform and in ether.

GALVUMET tablets are available in 3 strengths:

50 mg vildagliptin and 500 mg metformin hydrochloride
50 mg vildagliptin and 850 mg metformin hydrochloride
50 mg vildagliptin and 1,000 mg metformin hydrochloride

Each tablet contains the following excipients – hydroxypropyl cellulose, hypromellose, iron oxide yellow, iron oxide red, macrogol 4000, magnesium stearate, talc-purified, and titanium dioxide.

PHARMACOLOGY

Pharmacodynamics

GALVUMET combines two antihyperglycaemic agents with different mechanisms of action to improve glycaemic control in patients with type 2 diabetes (T2D): vildagliptin, a member of the DPP-4 (dipeptidyl-peptidase-4) inhibitor class and metformin hydrochloride, a member of the biguanide class.

Vildagliptin

Vildagliptin, a member of the islet enhancer class, 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. In patients with type 2 diabetes, administration of vildagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. Vildagliptin inhibition of DPP-4 results in increased fasting and postprandial endogenous levels of the incretin hormones GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide).

By increasing the endogenous levels of these incretin hormones, vildagliptin enhances the sensitivity of beta cells to glucose, resulting in improved glucose-dependent insulin secretion. Treatment with 50 to 100 mg daily in patients with T2D significantly improved markers of beta cell function. The degree of improvement in beta-cell function is dependent on the initial degree of impairment; in non-diabetic (normal glycaemic) individuals, vildagliptin does not stimulate insulin secretion or reduce glucose levels.

By increasing endogenous GLP-1 levels, vildagliptin enhances the sensitivity of alpha cells to glucose, resulting in more glucose-appropriate glucagon secretion. The reduction in inappropriate glucagon during meals in turn attenuates insulin resistance.

The enhanced increase in the insulin/glucagon ratio during hyperglycaemia (due to increased incretin hormone levels) results in a decrease in fasting and postprandial hepatic glucose production, leading to reduced glycaemia.

The known effect of increased GLP-1 levels to delay gastric emptying is not observed with vildagliptin treatment. In addition, a reduction in postprandial lipaemia that is not associated with vildagliptin's incretin mediated effect to improve islet function has been observed.

Metformin Hydrochloride

Metformin hydrochloride improves glucose tolerance in patients with T2D, lowering both basal and postprandial plasma glucose. Metformin hydrochloride decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin hydrochloride does not cause hypoglycaemia in either patients with T2D or normal subjects (except in special circumstances), and does not cause hyperinsulinaemia. With metformin hydrochloride therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Metformin hydrochloride stimulates intracellular glycogen synthesis by acting on glycogen synthase and increases the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

In humans, metformin hydrochloride has favourable effects on lipid metabolism, independent of its action on glycemia. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin hydrochloride reduces total cholesterol, LDLc and triglyceride levels.

Pharmacokinetics

Linearity

Vildagliptin

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 increased in an approximately dose-proportional manner over the therapeutic dose range.

Metformin Hydrochloride

Studies using single oral doses of metformin tablets indicate a lack of dose proportionality, due to increased absorption of metformin with increasing doses.

Absorption

In the bioequivalence studies of GALVUMET at three dose strengths (50 mg/500 mg, 50 mg/850 mg and 50 mg/1,000 mg), versus free combination of vildagliptin and metformin hydrochloride tablets at the corresponding doses, the area under the curve (AUC) and maximum concentration (C_{max}) of both the vildagliptin component and the metformin hydrochloride component of the GALVUMET tablets were demonstrated to be bioequivalent to that of free combination tablets.

Food does not affect the extent and rate of absorption of vildagliptin from GALVUMET. The C_{max} and AUC of the metformin hydrochloride component from GALVUMET were decreased by 26% and 7%, respectively when given with food. The absorption of metformin hydrochloride was also delayed as reflected by the T_{max} (2.0 to 4.0 hrs) when given with food. These changes in C_{max} and AUC are consistent but lower than those observed when metformin hydrochloride was given alone under fed conditions. The effects of food on the pharmacokinetics of both the vildagliptin component and metformin hydrochloride component of GALVUMET were similar to the pharmacokinetics of vildagliptin and metformin hydrochloride when given alone with food.

Vildagliptin

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).

Metformin Hydrochloride

The absolute bioavailability of a 500 mg metformin hydrochloride tablet given under fasting conditions is approximate 50 to 60%. Studies using single oral doses of metformin hydrochloride tablets 500 mg to 1,500 mg, and 850 mg to 2,550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin hydrochloride, as shown by approximately a 40% lower mean peak plasma concentration (C_{max}), a 25% lower area under the plasma concentration versus time curve, and a 35-minute prolongation of the time to peak plasma concentration (T_{max}) following administration of a single 850 mg tablet of metformin hydrochloride with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution

Vildagliptin

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 litres, suggesting extravascular distribution.

Metformin Hydrochloride

The apparent volume of distribution (V/F) of metformin hydrochloride following single oral doses of 850 mg averaged 654 ± 358 litres. Metformin hydrochloride is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin hydrochloride partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin hydrochloride, steady state plasma concentrations of metformin hydrochloride are reached within 24 to 48 hours and are generally < 1 microgram/mL. During controlled clinical studies of metformin hydrochloride, maximum metformin hydrochloride plasma levels did not exceed 5 micrograms/mL, even at maximum doses.

Metabolism

Vildagliptin

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.

Metformin Hydrochloride

Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism. In patients with significantly decreased renal function, the plasma half-life of metformin is prolonged and renal clearance is decreased.

Excretion and Elimination

Vildagliptin

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 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.

Metformin Hydrochloride

Intravenous single-dose studies in normal subjects demonstrate that metformin hydrochloride is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Special Populations

Elderly

Vildagliptin

In otherwise healthy elderly subjects (≥ 70 years), the overall exposure to vildagliptin (100 mg once daily) 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.

Metformin Hydrochloride

Limited data from controlled pharmacokinetic studies of metformin hydrochloride in healthy elderly subjects suggest that total plasma clearance of metformin hydrochloride is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin hydrochloride pharmacokinetics with aging is primarily accounted for by a change in renal function.

GALVUMET treatment should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.

Paediatric

No pharmacokinetic data are available in children.

Gender

Vildagliptin

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.

Metformin Hydrochloride

Metformin hydrochloride pharmacokinetic parameters did not differ significantly between normal subjects and patients with T2D when analysed according to gender (males=19, females-16). Similarly, in controlled clinical studies in patients with T2D, the antihyperglycaemic effect of metformin hydrochloride was comparable in males and females.

Obesity

Vildagliptin

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

Hepatic Impairment

Vildagliptin

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 decreased (20% and 8%, respectively), while the exposure to vildagliptin for subjects with severe impairment 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).

Metformin hydrochloride

No pharmacokinetic studies of metformin hydrochloride have been conducted in subjects with hepatic impairment.

Renal Impairment

Vildagliptin

In subjects with mild, moderate, and severe renal impairment, and patients with end stage renal disease (ESRD) on haemodialysis, systemic exposure to vildagliptin was increased (C_{max} 8% to 66%; AUC 32% to 134%) compared to subjects with normal renal function. Exposure to the inactive metabolite (LAY151) increased with increasing severity of renal impairment (AUC 1.6- to 6.7-fold). Changes in exposure to vildagliptin did not correlate with severity of renal impairment, whereas changes in exposure to the inactive metabolite did correlate. Elimination half-life of vildagliptin was not affected by renal impairment. Based on the evaluation of safety,

tolerability, and effectiveness of vildagliptin in patients enrolled in clinical trials whose GFR values were < 60 mL/min, no dosage adjustment is required in patients with mild renal impairment. The use of vildagliptin is not recommended in patients with moderate or severe renal impairment or in patients with ESRD on haemodialysis (see PRECAUTIONS Renal Impairment).

Metformin Hydrochloride

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin hydrochloride is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Race

Vildagliptin

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

Metformin Hydrochloride

No studies of metformin hydrochloride pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin hydrochloride in patients with T2D, the antihyperglycaemic effect was comparable in white (n=249), black (n=51) and Hispanic (n=24) patients.

CLINICAL TRIALS

Vildagliptin

More than 15,000 patients with T2D participated in double-blind, placebo- or active-controlled clinical trials 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 T2D or in combination in patients not adequately controlled by other antidiabetic medicinal products.

Overall, vildagliptin improved glycaemic control when given as monotherapy or when used in combination with metformin hydrochloride, as measured by clinically relevant reductions in HbA_{1c} and fasting plasma glucose from baseline at the study endpoint. When given as monotherapy or in combination with metformin hydrochloride in studies of up to 52 weeks in duration, these improvements in glucose homeostasis were durable.

Cardiac failure

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.

Cardiovascular risk

A meta-analysis of independently and prospectively adjudicated cardiovascular events from 25 phase III clinical studies of up to more than 2 years duration was performed. It involved 8956 patients with type 2 diabetes treated with vildagliptin and showed that vildagliptin treatment was not associated with an increase in cardiovascular risk. The composite endpoint of adjudicated CCV events [acute coronary syndrome (ACS), stroke or CCV death], was similar for vildagliptin versus combined active and placebo comparators [Mantel–Haenszel risk ratio 0.84 (95% confidence interval 0.63-1.12)] supporting the cardiovascular safety of vildagliptin. In total, 99 out of 8956 patients reported an event in the vildagliptin group vs 91 out of 6061 patients in the comparator group.

Metformin

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with metformin hydrochloride after failure of diet alone showed:

a significant reduction of the absolute risk of any diabetes-related complication in the metformin hydrochloride group (29.8 events/1,000 patient-years) versus diet alone (43.3 events/1,000 patient-years), p = 0.0023, and versus the combined sulfonylurea and insulin monotherapy groups (40.1 events/1,000 patient-years), p = 0.0034;

a significant reduction of the absolute risk of diabetes-related mortality: metformin hydrochloride 7.5 events/1,000 patient-years, diet alone 12.7 events/1,000 patient-years, p = 0.017;

a significant reduction of the absolute risk of overall mortality: metformin hydrochloride 13.5 events/1,000 patient-years versus diet alone 20.6 events/1,000 patient-years (p = 0.011), and versus the combined sulfonylurea and insulin monotherapy groups 18.9 events/1,000 patient-years (p = 0.021); and

a significant reduction in the absolute risk of myocardial infarction: metformin hydrochloride 11 events/1,000 patient-years, diet alone 18 events/1,000 patient-years (p = 0.01).

Vildagliptin combination therapy with metformin

The efficacy and safety of the separate components have previously been established and the efficacy and safety of the co-administration of the separate components have been evaluated in clinical studies. These clinical studies established an added benefit of vildagliptin in patients with inadequately controlled T2D while on metformin hydrochloride therapy. GALVUMET tablets were shown to be bioequivalent to the individual components.

In a double-blind, placebo-controlled trial (Study 2303; n=544) in patients with T2D whose hyperglycaemia was inadequately controlled on a maximum dose of metformin hydrochloride

alone, the addition of vildagliptin (50 mg once daily or 100 mg in divided doses) 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 continued on metformin hydrochloride alone. Group mean baseline HbA_{1c} (%) ranged from 8.3% (placebo plus metformin hydrochloride) to 8.4% (in both vildagliptin plus metformin hydrochloride groups). Vildagliptin combined with metformin hydrochloride 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 clinically meaningful and robust decrease in HbA_{1c} (defined as a decrease $\geq$ 0.7 % from baseline) was statistically significantly higher in both vildagliptin plus metformin hydrochloride groups (46% and 60%, respectively) versus the metformin hydrochloride plus placebo group (20%). Patients on the combination of vildagliptin plus metformin hydrochloride did not experience a meaningful change in body weight compared to baseline. After 24 weeks, there was a decrease from baseline for both systolic and diastolic blood pressure in the vildagliptin treatment groups combined with metformin hydrochloride. Mean changes from baseline were -2.0/-0.8 mmHg, -3.5/-2.2 mmHg, and -0.8/-0.1 mmHg, in patients receiving metformin hydrochloride combined with vildagliptin 50 mg once daily, vildagliptin 50 mg twice daily or placebo, respectively. The incidence of gastrointestinal side effects ranged from 10% to 15% in the vildagliptin plus metformin hydrochloride groups as compared to 18% in the metformin hydrochloride plus placebo group.

The effect of vildagliptin in combination with metformin hydrochloride was evaluated in another, double-blind, placebo-controlled clinical trial (Study 2204E1) lasting 52 weeks in total (12-week core study plus a 40-week extension) involving 132 patients with T2D on stable doses of metformin hydrochloride (1,500 mg to 3,000 mg daily). The addition of vildagliptin (50 mg once daily) to metformin hydrochloride resulted in an additional statistically significant reduction in mean HbA_{1c} (-0.6%) from baseline compared to placebo plus metformin hydrochloride (+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) and 58 of these patients completed the full 52-week treatment. At 52 weeks, mean change from baseline in HbA_{1c} was statistically significantly greater and sustained with vildagliptin (50 mg) plus metformin hydrochloride versus patients continued on metformin hydrochloride alone (between group difference of -1.1%) indicating a durable effect on glycaemic control. In contrast, glycaemic control in the metformin hydrochloride plus placebo group deteriorated over the course of the study.

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 body weight difference further increased.

In a long term, double-blind, active-controlled trial of 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 1-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 the study endpoint (2 years), the HbA_{1c} was similar to baseline values in both treatment groups and the body weight changes and hypoglycaemia differences were maintained.

In a 24-week trial (Study 2302) the efficacy of the fixed dose combination of vildagliptin and metformin (gradually titrated to a dose of 50 mg/500 mg twice daily or 50 mg/1,000 mg twice daily) as initial therapy in drug-naïve patients was evaluated. The mean HbA1c reductions were significantly greater with vildagliptin plus metformin combination therapy compared to either monotherapy. Vildagliptin/metformin 50 mg/1,000 mg twice daily reduced HbA1c by - 1.82% and vildagliptin/metformin 50 mg/500 mg twice daily by -1.61% from a mean baseline HbA1c of 8.6%. The decrease in HbA1c observed in patients with a baseline ≥10.0% was greater. Body weight decreased in all groups, with a mean reduction of -1.2 kg for both vildagliptin plus metformin combinations. The incidence of hypoglycaemia was similar across treatment groups (0% with vildagliptin plus metformin combinations and 0.7% with each monotherapy).

Combination with insulin

A 24-week randomized, double-blind, placebo-controlled trial (Study A23135) 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. The patients treated concomitantly with metformin were given separate doses of vildagliptin and metformin rather than the fixed dose combination tablets, and only a limited number of patients were treated with doses matching those available from Galvumet.

Vildagliptin in combination with insulin significantly decreased HbA1c compared with placebo. In the overall population, the placebo-adjusted mean reduction from a mean baseline HbA1c 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 weight were +0.2 kg and -0.7 kg in the vildagliptin and placebo groups, respectively.

Triple combination therapy with 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 a mean baseline HbA1c 8.8% was -0.76%.

INDICATIONS

For patients with Type 2 diabetes mellitus (T2DM):

GALVUMET is indicated as an adjunct to diet and exercise to improve glycaemic control in patients whose diabetes is not adequately controlled on metformin hydrochloride alone or who are already treated with the combination of vildagliptin and metformin hydrochloride, as separate tablets. Treatment should not be initiated with this fixed-dose combination.

GALVUMET is indicated in combination with a sulfonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled with metformin and a sulfonylurea.

GALVUMET is indicated as add-on to insulin as an adjunct to diet and exercise to improve glycaemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycaemic control.

CONTRAINDICATIONS

Hypersensitivity

GALVUMET is contraindicated in patients with known hypersensitivity to vildagliptin or metformin hydrochloride or to any of the excipients (see DESCRIPTION).

Renal Disease

GALVUMET is contraindicated in patients with renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥1.5 mg/dL (>135 micromol/L) in males and ≥ 1.4 mg/dL (> 110 micromol/L) in females or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicaemia (see DOSAGE and ADMINISTRATION and PRECAUTIONS).

Congestive Heart Failure

GALVUMET is contraindicated in patients with congestive heart failure requiring pharmacologic treatment (see PRECAUTIONS).

Metabolic acidosis

GALVUMET is contraindicated in patients with acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

Radiologic Studies

GALVUMET should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function (see PRECAUTIONS).

PRECAUTIONS

General

GALVUMET is not a substitute for insulin in patients requiring insulin. GALVUMET should not be used in patients with T1D or for the treatment of diabetic ketoacidosis.

Renal Impairment

GALVUMET should not be used in patients with renal failure or renal dysfunction, e.g. serum creatinine levels ≥ 1.5 mg/dL (> 135 micromol/L) in males and ≥ 1.4 mg/dL (> 110 micromol/L) in females (see CONTRAINDICATIONS).

Monitoring of Renal Function

Metformin hydrochloride is known to be substantially excreted by the kidney and the risk of metformin hydrochloride accumulation and lactic acidosis increases with the degree of renal function impairment. Patients with serum creatinine levels above the ULN for their age should not receive GALVUMET. Since advancing age is associated with reduced renal function, GALVUMET should be carefully titrated in the elderly to establish the minimum dose for adequate glycaemic effect, and renal function should be monitored regularly. Also, special caution should be exercised where renal function may become impaired, for example when initiating antihypertensive or diuretic therapy or when starting treatment with an NSAID. Renal function should be assessed and verified as normal before the initiation of GALVUMET, then at least once a year in patients with normal renal function and at least two to four times a year in patients with serum creatinine levels at the ULN. Additionally, patients in whom renal dysfunction is anticipated should have their renal function assessed more frequently. GALVUMET should be discontinued if evidence of renal impairment is present.

Concomitant Medications that May Affect Renal Function or Metformin Hydrochloride Disposition

Concomitant medications that may affect renal function, result in significant haemodynamic change or interfere with the disposition of metformin hydrochloride, such as cationic drugs that are eliminated by renal tubular secretion should be used with caution (see INTERACTIONS WITH OTHER MEDICINES).

Cardiac failure

GALVUMET is contraindicated in patients with congestive heart failure requiring pharmacologic treatment, which may potentially interact with metformin hydrochloride (see CONTRAINDICATIONS and INTERACTIONS WITH OTHER MEDICINES).

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 results are inconclusive (see 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.

Hepatic Impairment

Vildagliptin, and hence GALVUMET is not recommended in patients with clinical or laboratory evidence of hepatic impairment, including patients with pre-treatment ALT or AST >2.5x the ULN.

Since impaired hepatic function has been associated with some cases of lactic acidosis (a risk associated with metformin hydrochloride), GALVUMET should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Liver Enzyme Monitoring

Rare cases of hepatic dysfunction (including hepatitis) have been reported with vildagliptin. 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 GALVUMET. GALVUMET is not recommended in patients with a pre-treatment ALT or AST >2.5x the ULN. LFTs should be monitored during GALVUMET 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 up thereafter with frequent liver function tests until the abnormality/abnormalities return to normal. Should an increase in AST or ALT of 3x the ULN or greater persist, withdrawal of therapy with GALVUMET is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue GALVUMET and contact their physician immediately. Following withdrawal of treatment with GALVUMET and LFT normalisation, GALVUMET should not be reinitiated. GALVUMET is not recommended in patients with hepatic impairment.

Lactic Acidosis

Lactic acidosis is a very rare but serious metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors, such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any conditions associated with hypoxia (see CONTRAINDICATIONS).

Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, treatment with the medicinal product should be discontinued and the patient hospitalised immediately (see OVERDOSAGE).

Paediatric use

The safety and effectiveness of GALVUMET in paediatric patients have not been established. Therefore, GALVUMET is not recommended for use in children below 18 years of age.

Use in the Elderly (≥ 65 Years)

As metformin is excreted via the kidney, and elderly patients have a tendency to decreased renal function, elderly patients taking GALVUMET should have their renal function monitored regularly. GALVUMET should only be used in elderly patients with normal renal function (see CONTRAINDICATIONS).

Effects on fertility

No studies have been conducted with vildagliptin and metformin in combination to evaluate potential effects on fertility. Fertility studies have been performed with vildagliptin in rats at doses producing exposures equivalent to up to 160 times the human dose and have revealed no evidence of impaired male or female fertility or early embryonic development due to vildagliptin. Fertility of male or female rats was also unaffected by metformin administration at doses up to 600 mg/kg/day, or approximately 3-times the maximum recommended daily human dose on a body surface area basis.

Use in pregnancy (Category C)

Embryofetal development (teratology) studies have been conducted in rats and rabbits with the combination of vildagliptin and metformin hydrochloride in a 1:10 ratio There was no evidence of teratogenicity at oral doses yielding plasma exposure levels up to *ca* 14-20 times (rats) or 1.3-2 times (rabbits) that anticipated in patients at the maximum recommended clinical dose. An increase in the incidence of incomplete ossification in rats and an increase in early resorptions in rabbits were observed at these doses.

However, there are no adequate and well-controlled studies in pregnant women, and animal studies are not always predictive of the human response. Therefore GALVUMET should not be used during pregnancy unless the potential benefit justifies the potential risk to the foetus.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin monotherapy be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Use in lactation

No studies have been conducted with the combined components of GALVUMET. Metformin is excreted into human breast milk. It is not known whether vildagliptin is excreted in human milk or not. GALVUMET should not be administered to breast-feeding women.

Carcinogenicity

No carcinogenicity studies have been conducted with the combined components of GALVUMET.

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 (males) to 80 (females) times human exposure in mice. No effect levels of *ca* 80 to 160 times the human exposure were

established in rats. Mammary tumour incidence was increased in female mice at approximately 185 times the maximum anticipated human exposures 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.

Long-term carcinogenicity studies with metformin were performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 and 1,500 mg/kg/day respectively. These doses are approximately three to four times the recommended human daily dose on a body surface area basis. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. However, an increased incidence of benign stromal uterine polyps was seen in female rats treated with 900 mg/kg/day.

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.

Metformin was not mutagenic in the bacterial reverse mutation assay, gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes), or *in vivo* micronuclei formation test (mouse bone marrow).

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 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 $\geq$ 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 clinical trial programme.

Administration of Intravascular Iodinated Contrast Materials

GALVUMET should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function and increase the risk of lactic acidosis. In patients undergoing such studies, GALVUMET should be temporarily discontinued at the time of or prior to the procedure, withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

Hypoxic States

Cardiovascular collapse (shock), acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxaemia have been associated with lactic acidosis and may also cause pre-renal azotmeia. If such events occur in patients receiving GALVUMET therapy, the medication should be promptly discontinued.

Surgical Procedures

Use of GALVUMET should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Alcohol Intake

Alcohol is known to potentiate the effect of metformin hydrochloride on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving GALVUMET.

Vitamin B_{12} Levels

Metformin has been associated with a decrease in serum vitamin B_{12} levels without clinical manifestations, in approximately 7% of patients. Such a decrease is very rarely associated with anaemia and appears to be rapidly reversible with discontinuation of metformin hydrochloride and/or vitamin B_{12} supplementation. Measurement of haematological parameters on at least an annual basis is advised for patients receiving GALVUMET and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (e.g., those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurements at minimally two-to-three-year intervals may be useful.

Change in Clinical Status of Patients with Previously Controlled T2DM

A patient with T2DM previously well-controlled on GALVUMET who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should promptly be evaluated for ketoacidosis and/or lactic acidosis. If acidosis of either form occurs, GALVUMET must be stopped immediately and appropriate measures initiated.

Hypoglycaemia

Hypoglycaemia does not usually occur in patients receiving GALVUMET alone, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or ethanol use. Elderly, debilitated or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are susceptible to hypoglycaemic effects. Hypoglycaemia may be difficult to recognize in the elderly and in people taking beta-adrenergic blocking drugs.

Loss of Control of Blood Glucose

When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, surgery, etc., a temporary loss of glycaemic control may occur. At such times, it may

be necessary to withhold GALVUMET and temporarily administer insulin. GALVUMET may be reinstituted after the acute episode is resolved.

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 are prone to dizziness should therefore avoid driving vehicles or using machines.

INTERACTIONS WITH OTHER MEDICINES

No clinically relevant pharmacokinetic interactions have been observed when vildagliptin (100 mg once daily) was co-administered with metformin hydrochloride (1,000 mg once daily). Drug interactions for each component of GALVUMET have been extensively studied. However, the concomitant use of the active substances in patients in clinical studies and in widespread clinical use has not resulted in any unexpected interactions.

The following statements reflect the information available on the individual active substances (vildagliptin and metformin).

Vildagliptin

Vildagliptin has low potential for drug interactions. Since vildagliptin is not a cytochrome P (CYP) 450 enzyme substrate nor does it inhibit or induce 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 CYP 1A2, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1, and CYP 3A4/5. Drug-drug interaction studies were conducted with commonly co-prescribed medications for patients with T2DM or medications with a narrow therapeutic window. As a result of these studies no clinically relevant interactions with other oral antidiabetics (glibenclamide, pioglitazone, metformin hydrochloride), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin.

Metformin Hydrochloride

Furosemide

Furosemide increased C_{max} and blood AUC of metformin with no change in renal clearance of metformin. Metformin decreased C_{max}, blood AUC of furosemide, with no change in renal clearance of furosemide.

Nifedipine

Nifedipine increased absorption, C_{max} and AUC of metformin, and increased excretion of metformin in urine. Metformin had minimal effects on nifedipine.

Glyburide

Glyburide produced no changes in metformin PK/PD parameters. Decreases in C_{max}, blood AUC of glyburide were observed, but were highly variable. Therefore the clinical significance of this finding was unclear.

Cationic drugs

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential to interact with metformin by competing for common renal tubular transport systems. Thus, with cimetidine increases in metformin plasma/blood concentration and AUC were observed to be 60% and 40% respectively. Metformin had no effect on cimetidine PK. Although such interactions remain theoretical (except for cimetidine), careful monitoring of patients and doses of metformin and such medications are recommended.

Other

Certain drugs tend to cause hyperglycaemia and may lead to loss of glycaemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. Close monitoring of glycaemic control and metformin dose adjustments are recommended when such drugs are administered or withdrawn for these patients.

There is an increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic impairment) due to metformin. Consumption of alcohol and medicinal products containing alcohol should be avoided (see PRECAUTIONS).

ADVERSE EFFECTS

The data presented here relate to the administration of vildagliptin and metformin as a free or fixed dose combination.

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 with vildagliptin. 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 studies lasting up to 24 weeks, 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.

In clinical studies with the combination of vildagliptin + metformin, 0.4% of patients withdrew due to adverse reactions in the vildagliptin 50 mg once daily + metformin treatment group, and no withdrawal due to adverse reactions was reported in either the vildagliptin 50 mg bid + metformin or the placebo + metformin treatment groups.

In clinical studies, 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 and metformin (0.4%). No severe hypoglycaemic events were reported in the vildagliptin arms.

Vildagliptin is weight-neutral when administered in combination with metformin.

Gastrointestinal adverse reactions including diarrhoea and nausea, are known to occur very commonly during the introduction of metformin hydrochloride. In the vildagliptin monotherapy clinical program (n = 2,264) where vildagliptin was administered 50 mg once daily, 50 mg twice daily, or 100 mg once daily, the rate of diarrhoea was 1.2%, 3.5% and 0.8 %, respectively, and the rate of nausea was 1.7%, 3.7% and 1.7%, respectively, as compared to 2.9% for both in the placebo group (n = 347) and 26.2% and 10.3%, respectively, in the metformin hydrochloride group (n = 252).

Overall, gastrointestinal symptoms were reported in 13.2% (50 mg once daily or twice daily) of patients treated with the combination of vildagliptin and metformin hydrochloride compared to 18.1% of patients treated with metformin hydrochloride alone.

Adverse reactions reported in patients who received vildagliptin in double-blind studies as an add-on to metformin and as monotherapy, are listed in **Table 1** for each indication, 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, < 1/1,000); very rare (< 1/10,000), including isolated reports. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Other adverse reactions reported in patients who received vildagliptin 50 mg once daily (n=233) or 50 mg twice daily (n=183) as add-on therapy to metformin compared to placebo plus metformin in double-blind studies

Nervous system disorders	
Common	Tremor, dizziness, headache

Long-term clinical studies of up to more than 2 years in duration, did not show any additional safety signals or unforeseen risks when vildagliptin was added on to metformin.

Combination with Insulin

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

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

Uncommon: Diarrhoea, flatulence

The overall incidence of withdrawals 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 arms of the 24-week study investigating vildagliptin as add-on to insulin treatment (with or without metformin) is shown in Table 2.

Table 2 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 SU

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 3 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**

Vildagliptin

Adverse reactions for vildagliptin component from monotherapy double blind studies are presented in Table 4.

Table 4: Adverse reactions reported in patients who received vildagliptin 50 mg once daily (n=409) or 50 mg twice daily (n=1,373) 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

None of the adverse reactions reported for the vildagliptin monotherapy were observed at clinically significantly higher rates when vildagliptin was administered concomitantly with metformin.

The overall incidence of withdrawal from monotherapy studies due to adverse reactions was no greater for patients treated with vildagliptin at a dose of 50 mg once daily (0.2%) or vildagliptin at a dose of 50 mg twice daily (0.1%) than for placebo (0.6%) or comparators (0.5%).

In monotherapy studies, hypoglycaemia was uncommon reported in 0.5% (2 of 409) of patients treated with vildagliptin 50 mg once daily and 0.3% (4 of 1,373) of patients treated with vildagliptin 50 mg twice daily compared to 0.2% (2 of 1,082) of patients in the groups treated with an active comparator or placebo, with no serious or severe events reported. Vildagliptin is weight neutral when administered as monotherapy.

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

Post-marketing Experience with vildagliptin

During post-marketing experience the following additional adverse drug reaction has been reported:

Rare cases of hepatitis reversible upon drug discontinuation
Frequency not known*:

- Urticaria, bullous and exfoliative skin lesions, including bullous pemphigoid

- Pancreatitis
- Arthralgia, sometimes severe.

*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".

Metformin Hydrochloride

Known adverse reactions for the metformin are summarized in Table 5.

Table 5: Known adverse reactions for metformin

Metabolism and nutrition disorders		
	Very rare	Decrease of vitamin B12 absorption*, lactic acidosis
Nervous system disorders		
	Common	Metallic taste
Gastrointestinal disorders		
	Very common	Flatulence, nausea, vomiting, diarrhoea, abdominal pain, loss of appetite
Hepatobiliary disorders		
	Very rare	Liver function test abnormalities, hepatitis**
Skin and subcutaneous tissue disorders		
	Very rare	Skin reactions such as erythema, pruritus, urticaria

**A decrease of vitamin B12 absorption with decrease of serum levels has very rarely been observed in patients treated long-term with metformin and appears to generally not be of clinical significance. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.*

***Isolated cases of liver function test abnormalities or hepatitis resolving upon metformin discontinuation have been reported.*

Gastrointestinal adverse effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that metformin be taken in 2 daily doses during or after meals. A slow increase in the dose may also improve gastrointestinal tolerability.

DOSAGE AND ADMINISTRATION

Life threatening lactic acidosis can occur due to accumulation of metformin. The main risk factor is renal impairment, other risk factors include old age associated with reduced renal function and high doses of metformin above 2 g per day.

To minimise the risk of lactic acidosis, only one strength of GALVUMET should be prescribed and used at any one time. Patients should also be advised to discard their previous metformin medication when initiated on GALVUMET.

Adults

The use of antihyperglycaemic therapy in the management of T2D should be individualized on the basis of effectiveness and tolerability. The recommended starting dose of GALVUMET should be based on the patient's current regimen of vildagliptin and/or metformin hydrochloride. GALVUMET should be given with meals to reduce the gastrointestinal side effects associated with metformin hydrochloride. When using GALVUMET the maximum daily dose of vildagliptin (100 mg) should not be exceeded.

Starting dose for patients inadequately controlled on metformin hydrochloride monotherapy:

Based on the patient's current dose of metformin hydrochloride, GALVUMET may be initiated at either the 50 mg/500 mg, 50 mg/850 mg or 50 mg/1,000 mg tablet strength twice daily.

Starting dose for patients switching from combination therapy of vildagliptin plus metformin hydrochloride as separate tablets:

GALVUMET may be initiated with either the 50 mg/500 mg, 50 mg/850 mg or 50 mg/1,000 mg tablet strength based on the dose of vildagliptin or metformin already being taken.

Use in combination with a sulfonylurea or with insulin:

The dose of GALVUMET should provide vildagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken.

OVERDOSAGE

Accidental overdose resulting from the continuance of previously prescribed products may occur. To avoid accidental overdose, patients should be advised to discard their previous metformin medication when prescribed with GALVUMET.

Symptoms and treatment

Vildagliptin

In healthy subjects (seven to fourteen subjects per treatment group), 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 400 mg, there were three cases of muscle pain, and individual cases of mild and transient paraesthesia, fever, oedema and transient increase in lipase levels (2x ULN). At 600 mg, one subject experienced oedema of the hands and feet, and an excessive increase in creatine phosphokinase (CPK) levels, accompanied by elevations of aspartate aminotransferase (AST), C-reactive protein, and myoglobin. Three additional subjects in this

dose group presented with oedema of both feet, accompanied by paraesthesia in two cases. All symptoms and laboratory abnormalities resolved after study drug discontinuation.

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

Metformin Hydrochloride

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycaemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin hydrochloride overdose cases. Metformin hydrochloride is dialyzable with a clearance of up to 170 mL/min under good haemodynamic conditions. Therefore, haemodialysis may be useful for removal of the accumulated drug from patients in whom metformin hydrochloride overdosage is suspected.

In the event of overdosage, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms. Contact the Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Presentation

GALVUMET is available in three strengths:

50 mg/500 mg: light yellow, ovaloid bevelled edge, film-coated tablet imprinted with "NVR" on one side and "LLO" on the other side.

50 mg/850 mg: yellow, ovaloid bevelled edge, film-coated tablet imprinted with "NVR" on one side and "SEH" on the other side.

50 mg/1,000 mg: dark yellow, ovaloid bevelled edge, film-coated tablet imprinted with "NVR" on one side and "FLO" on the other side.

GALVUMET is available in blister packs containing 10, 30, 60, 120, 180 or 360 tablets.

Some pack sizes may not be marketed.

Storage

Do not store above 30°C. Store in the original package.

NAME AND ADDRESS OF THE SPONSOR

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® = Registered Trademark

POISON SCHEDULE OF THE MEDICINE

Schedule 4 - Prescription Only Medicine

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