

GALVUS MET[®]

Vildagliptin / Metformin Hydrochloride 50 mg/850 mg, 50 mg/1,000 mg tablets

Qualitative and quantitative composition

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

Metformin hydrochloride: Imidodicarbinimidic, N,N-dimethyl-, monohydrochloride

Two strengths are available. One tablet of Galvus Met contains:

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

For a full list of excipients, see List of excipients.

Pharmaceutical form

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

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

Clinical particulars

Therapeutic indications

Galvus Met is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus whose diabetes is not adequately controlled on metformin hydrochloride or vildagliptin alone or who are already treated with the combination of vildagliptin and metformin hydrochloride, as separate tablets.

Dosage and method of administration

The use of antihyperglycaemic therapy in the management of type 2 diabetes should be individualized on the basis of effectiveness and tolerability. In using Galvus Met do not exceed the maximum daily dose of vildagliptin (100 mg).

The recommended starting dose of Galvus Met should be based on the patient's current regimen of vildagliptin and/or metformin hydrochloride. Galvus Met should be given with meals to reduce the gastrointestinal side effects associated with metformin hydrochloride.

Starting dose for patients inadequately controlled on vildagliptin monotherapy

Based on the usual starting doses of metformin hydrochloride (850 mg once daily), Galvus Met may be initiated at the 50 mg/1000mg tablet strength once daily and gradually titrated after assessing adequacy of therapeutic response.

Starting dose for patients inadequately controlled on metformin hydrochloride monotherapy

Based on the patient's current dose of metformin hydrochloride, Galvus Met may be initiated at either the 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

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

Patients with renal impairment

Galvus Met 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 and Special warnings and precautions).

Patients with hepatic impairment

Galvus Met is not recommended in patients with clinical or laboratory evidence of hepatic impairment including patients with a pre-treatment ALT or AST >2.5X the upper limit of normal (see Special warnings and precautions for use).

Elderly

As metformin is excreted via the kidney, and elderly patients have a tendency to decreased renal function, elderly patients taking Galvus Met should have their renal function monitored regularly. Galvus Met should only be used in elderly patients with normal renal function (see Contraindications and Special warnings and precautions for use).

Paediatric patients

Safety and effectiveness of Galvus Met in paediatric patients have not been established. Therefore, Galvus Met is not recommended for use in children below 18 years of age.

Contraindications

Hypersensitivity

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

Renal disease

Galvus Met 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 method of administration and Special warnings and precautions for use).

Congestive heart failure

Galvus Met is contraindicated in patients with congestive heart failure requiring pharmacologic treatment (see Special warnings and precautions for use).

Diabetic ketoacidosis

Galvus Met 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

Galvus Met 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 Special warnings and precautions for use).

Special warnings and precautions for use

Galvus Met

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

Vildagliptin

Hepatic impairment

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.

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 Galvus Met. Galvus Met is not recommended in patients with a pre-treatment ALT or AST >2.5X the upper limit of normal. LFTs should be monitored during Galvus Met treatment at three-month intervals during the first year and periodically thereafter. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of 3 X upper limit of normal or greater persist, withdrawal of therapy with Galvus Met is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue Galvus Met and contact their physician immediately. Following withdrawal of treatment with Galvus Met and LFT normalisation, Galvus Met should not be reinitiated.

Galvus Met is not recommended in patients with hepatic impairment.

Metformin Hydrochloride

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 also Contraindications and Interactions with other medicinal products and other forms of interaction).

Diagnosis of lactic acidosis

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 Overdose).

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 upper limit of normal for their age should not receive Galvus Met. Since advancing age is associated with reduced renal function, Galvus Met 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 Galvus Met, 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 upper limit of normal. Additionally, patients in whom renal dysfunction is anticipated, should have their renal function assessed more frequently. Galvus Met 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 Interaction with other medicinal products and other forms of interaction).

Administration of intravascular iodinated contrast materials

Galvus Met 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, Galvus Met should be temporarily discontinued at the time of or prior to the procedure, withheld for 48 hours subsequent to the procedure and reinstated 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 prerenal azotemia. If such events occur in patients receiving Galvus Met therapy, the medication should be promptly discontinued.

Surgical procedures

Use of Galvus Met 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 Galvus Met.

Impaired hepatic function

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

Vitamin B₁₂ levels

The metformin component of Galvus Met has been associated with a decrease in serum vitamin B₁₂ levels without clinical manifestations, in approximately 7% of patients. Such decrease, is very rarely associated with anaemia and appears to be rapidly reversible with discontinuation of metformin hydrochloride and/or vitamin B₁₂ supplementation.

Measurement of haematological parameters on at least an annual basis is advised for patients receiving Galvus Met and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (e.g., those with inadequate vitamin B₁₂ or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B₁₂ levels. In these patients, routine serum vitamin B₁₂ measurements at minimally two-to-three-year intervals may be useful.

Change in clinical status of patients with previously controlled type 2 diabetes

A patient with type 2 diabetes previously well-controlled on Galvus Met 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, Galvus Met must be stopped immediately and appropriate measures initiated.

Hypoglycaemia

Hypoglycaemia does not usually occur in patients receiving Galvus Met 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 Galvus Met and temporarily administer insulin. Galvus Met may be reinstated after the acute episode is resolved.

Interaction with other medicinal products and other forms of interaction Galvus Met

No clinically relevant pharmacokinetic interaction was observed when vildagliptin (100 mg once daily) was co-administered with metformin hydrochloride (1,000 mg once daily). Drug interactions for each component of Galvus Met has 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 a low potential for drug interactions. Since vildagliptin is not a cytochrome P (CYP) 450 enzyme substrate nor does it inhibit nor induces CYP 450 enzymes, it is not likely to interact with co-medications that are 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 type 2 diabetes or medications with a narrow therapeutic window. As a result of these studies no clinically relevant interactions with other oral antidiabetics (glibenclamide, pioglitazone, metformin hydrochloride), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin.

Metformin Hydrochloride

The following is known for metformin component:

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 for interaction 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 produce 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 insufficiency) due to the metformin active substance of Galvus Met. Avoid consumption of alcohol and medicinal products containing alcohol. (see Special warnings and precautions).

Pregnancy and lactation

Pregnancy

Fertility studies have been performed with vildagliptin in rats at doses producing exposures equivalent to up to 200 times the human dose and have revealed no evidence of impaired fertility or early embryonic development due to vildagliptin. Embryofetal development (teratology) studies have been conducted in rats and rabbits with the combination of vildagliptin and metformin hydrochloride in a 1:10 ratio and produced no evidence of teratogenicity in either species. There are, however, no adequate and well-controlled studies in pregnant women and therefore, Galvus Met should not be used during pregnancy unless the potential benefit justifies the potential risk to the foetus. Animal studies are not always predictive of human response.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well 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.

Lactation

No studies have been conducted with the combined components of Galvus Met. As it is not known whether vildagliptin and/or metformin hydrochloride is excreted in human milk Galvus Met should not be administered to breast-feeding women.

Effects on ability to drive and use machines

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

Adverse effects

Galvus Met

There have been no therapeutic clinical trials conducted with Galvus Met. However, bioequivalence of Galvus Met with co-administered vildagliptin and metformin has been demonstrated (see Pharmacokinetic properties). The data presented here relate to the co-administration of vildagliptin and metformin, where vildagliptin has been added to metformin. There have been no studies of metformin added to vildagliptin.

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 trials up to 24 weeks in duration, the incidence of ALT or AST elevations $\geq 3 \times$ 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 trials with the combination of vildagliptin + metformin, 0.4% of patients withdrew due to adverse reactions in the vildagliptin 50 mg once daily + metformin treatment group, and no withdrawal due to adverse reactions was reported in either the vildagliptin 50 mg bid + metformin or the placebo + metformin treatment groups.

In clinical trials, the incidence of hypoglycaemia was uncommon in patients receiving vildagliptin 50 mg once daily in combination with metformin (0.9%), patients receiving vildagliptin 50 mg twice daily in combination with metformin (0.5%) and in patients receiving placebo and metformin (0.4%). No severe hypoglycemic 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 add-on to metformin and as monotherapy, are listed below, for each indication, by system organ class and absolute frequency. Frequencies are defined as: very common ($\geq 1/10$); common ($\geq 1/100, < 1/10$); uncommon ($\geq 1/1,000, < 1/100$); rare ($\geq 1/10,000, < 1/1,000$); very rare ($< 1/10,000$), including isolated reports. Within each frequency grouping, adverse 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 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.

Vildagliptin

Adverse reactions for vildagliptin component from monotherapy double blind studies are presented in Table 2.

Table 2: 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 significant higher rates when vildagliptin was administered concomitantly with metformin.

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

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

Vildagliptin is weight neutral when administered as monotherapy.

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

Post-marketing Experience

During post-marketing experience the following additional adverse drug reaction has been reported (frequency not known): urticaria.

Metformin Hydrochloride

Known adverse reactions for metformin component are summarized in Table 3.

Table 3: 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	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 been very rarely observed in patients treated long-term with metformin and appears generally to be without 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.

Overdose

Signs and symptoms

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 feet and hands, and an excessive increase in creatine phosphokinase (CPK) levels, accompanied by elevations of aspartate aminotransferase (AST), C-reactive protein, and myoglobin. Three additional subjects in this dose group presented with oedema of both feet,

accompanied by paraesthesia in two cases. All symptoms and laboratory abnormalities resolved after study drug discontinuation.

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 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.

Pharmacological properties

Pharmacodynamic properties

Galvus Met

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

There have been no clinical efficacy studies conducted with Galvus Met. However, the efficacy and safety of the separate components have been previously established and the co-administration of the separate components have been evaluated for efficacy and safety in clinical studies. These clinical studies established an added benefit of vildagliptin in patients with inadequately controlled type 2 diabetes while on metformin hydrochloride therapy.

In a double-blind, placebo-controlled trial in patients with type 2 diabetes whose hyperglycaemia was inadequately controlled on a maximal 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 were 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 ≥ 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 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 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). 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 24 week trial (LAF2354) vildagliptin (50 mg bid) was compared to pioglitazone (30 mg qd) in patients inadequately controlled with metformin. 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. Patients 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 trial of up to more than 2 years (LAF2308), vildagliptin (100 mg/day) was compared to glimepiride (up to 6 mg/day) in patients 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 hypoglycemia 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 hypoglycemia differences were maintained.

Vildagliptin

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

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

By increasing the endogenous levels of these incretin hormones, vildagliptin enhances the sensitivity of beta cells to glucose, resulting in improved glucose-dependent insulin secretion. Treatment with 50 to 100 mg daily in patients with type 2 diabetes significantly improved markers of beta cell function. The degree of improvement in beta-cell function is dependent on the initial degree of impairment; in non-diabetic (normal glycaemic) individuals, vildagliptin does not stimulate insulin secretion or reduce glucose levels.

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

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

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

More than 15,000 patients with type 2 diabetes participated in double-blind, placebo- or active-controlled clinical trials of up to more than 2 years 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.

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 study endpoint. When given as monotherapy or in combination with metformin hydrochloride in studies of up to 52 weeks duration, these improvements in glucose homeostasis were durable.

Metformin Hydrochloride

Metformin hydrochloride improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin hydrochloride decreases hepatic glucose production, decrease intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin hydrochloride does not produce hypoglycaemia in either patients with type 2 diabetes 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 increase the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

In humans, independently of its action on glycaemia, metformin hydrochloride has favourable effects on lipid metabolism. 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.

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 sulphonylurea 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 sulphonylurea and insulin monotherapy groups 18.9 events/1,000 patient-years ($p=0.021$)
- 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 ($p=0.01$)

Pharmacokinetic properties

Absorption

Galvus Met

In the bioequivalence studies of Galvus Met 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 Galvus Met 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 Galvus Met. The C_{max} and AUC of the metformin hydrochloride component from Galvus Met 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 when given alone under fed conditions. The effects of food on the pharmacokinetics of both the vildagliptin component and metformin hydrochloride component of Galvus Met 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. Coadministration with food slightly decreases the rate of absorption of vildagliptin, as characterized by a 19% decrease in peak concentrations, and a delay in the time to peak plasma concentration to 2.5 hours. There is no change in the extent of absorption, and food does not alter the overall exposure (AUC).

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 (AUC), and a 35 minute prolongation of 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 decrease is unknown.

Linearity

Vildagliptin is rapidly absorbed with an absolute oral bioavailability of 85%. Peak plasma concentrations for vildagliptin and the area under the plasma concentration versus time curve (AUC) increased in an approximately dose-proportional manner over the therapeutic dose range.

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 L, 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 L. 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 trials 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.

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 L/hour and 13 L/hour, respectively. The mean elimination half-life after intravenous administration is approximately 2 hours. The elimination half-life after oral administration is approximately 3 hours and is independent of dose.

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) nor 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

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 type 2 diabetes when analyzed according to gender (males=19, females=16). Similarly, in controlled clinical studies in patients with type 2 diabetes, 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 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.

Metformin Hydrochloride

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

Renal Impairment

Vildagliptin

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

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.

Elderly

Vildagliptin

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.

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.

Galvus Met 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 available.

Ethnic Group

Vildagliptin

There was 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 type 2 diabetes, the antihyperglycemic effect was comparable in whites (n=249), blacks (n=51) and Hispanics (n=24).

Preclinical safety data

Animal studies of up to 13-week duration have been conducted with the combined substances in Galvus Met. No new toxicities associated with the combination were identified. The following data are findings from studies performed with vildagliptin or metformin individually.

Vildagliptin

A two-year carcinogenicity study was conducted in rats at oral doses up to 900 mg/kg (approximately 200 times the human exposure at the maximum recommended dose). No increases in tumour incidence attributable to vildagliptin were observed. A two-year carcinogenicity study was conducted in mice at oral doses up to 1,000 mg/kg (up to 240 times the human exposure at the maximum recommended dose). Mammary tumour incidence was increased in female mice at approximately 150 times the maximum anticipated human exposure to vildagliptin; it was not increased at approximately 60 times the maximum human exposure. The incidence of haemangiosarcoma was increased in male mice treated at 42 to 240 times the maximum human exposure to vildagliptin and in female mice at 150 times the maximum human exposure. No significant increases in haemangiosarcoma incidences were observed at approximately 16 times the maximum human exposure to vildagliptin in males and approximately 60 times the maximum human exposure in females.

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

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

Metformin Hydrochloride

Preclinical data on metformin reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

Long-term carcinogenicity studies with metformin hydrochloride have been performed in rats (dosing duration 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1,500 mg/kg/day, respectively. These doses are both approximately four times the maximum recommended human daily dose of 2,000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin hydrochloride was found in either male or female mice. Similarly, there was no tumourigenic potential observed with metformin hydrochloride in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There was no evidence of mutagenic potential of metformin hydrochloride in the following *in vitro* tests: Ames test (*S. typhimurium*), and gene mutation test (mouse lymphoma cells) or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Pharmaceutical particulars

List of excipients

Ferric oxide red, ferric oxide yellow, hypromellose, hydroxypropylcellulose, magnesium stearate, polyethylene glycol, and talc.

Incompatibilities

Not applicable.

Shelf life

2 years.

Special precautions for storage

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

Galvus Met must be kept out of the reach and sight of children.

Nature and contents of container

Alu/Alu blister packs containing 10, 30, 60, 120, 180 and 360 film-coated tablets..

Instructions for use and handling, and disposal

No special requirements.

Medicine classification

Prescription Medicine

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