NOVARTIS

Galvusmet®

Composition

Active substances: Vildagliptin and metformin hydrochloride

Excipients: Tableting excipients

Pharmaceutical form and quantity of active substance per unit

Film-coated tablets containing:

- 50 mg vildagliptin and 500 mg metformin hydrochloride, or
- 50 mg vildagliptin and 850 mg metformin hydrochloride, or
- 50 mg vildagliptin and 1000 mg metformin hydrochloride

Indications / Potential uses

Galvusmet is indicated as an adjunct to diet and exercise in patients with type 2 diabetes mellitus whose blood glucose is not adequately controlled on metformin hydrochloride or vildagliptin alone, or in patients already being treated with a free combination of metformin hydrochloride and vildagliptin.

Dosage and Administration

Antidiabetic treatment should be individualized on the basis of effectiveness and tolerability. When using Galvusmet, do not exceed the maximum recommended daily dose of 100 mg vildagliptin.

The recommended starting dose of Galvusmet should be based on the current regimen of vildagliptin and/or metformin. Galvusmet should be given with meals to reduce the gastrointestinal adverse effects of metformin.

Starting dose for patients inadequately controlled on vildagliptin monotherapy

Based on the usual starting dose of metformin (daily dose: 500–1000 mg), Galvusmet should be initiated at the 50 mg / 500 mg or 50 mg / 850 mg tablet strength twice daily, with the dose of metformin being gradually titrated based on an assessment of the therapeutic response.

Starting dose for patients inadequately controlled on metformin monotherapy

Based on the current dose of metformin, Galvusmet should be initiated at either the 50 mg / 500 mg, 50 mg / 850 mg or 50 mg / 1000 mg tablet strength twice daily.

Starting dose for patients switching to Galvusmet from the free combination of metformin and vildagliptin

Based on the current dose of metformin or vildagliptin, Galvusmet should be initiated at either the 50 mg / 500 mg, 50 mg / 850 mg or 50 mg / 1000 mg tablet strength.

Patients with renal impairment

Galvusmet should not be used in patients with renal failure or renal dysfunction (creatinine clearance ≤ 60 ml/minute; see **Contraindications** and **Warnings and Precautions**).

Patients with hepatic impairment

Galvusmet is not recommended for use in patients with hepatic dysfunction, including patients with pre-treatment AST or ALT > 2.5 × ULN (see **Warnings and Precautions**).

Elderly patients

Metformin is excreted via the kidneys, and elderly patients have a tendency to decreased renal function. Therefore, elderly patients taking Galvusmet should have their renal function monitored regularly. Galvusmet should only be used in elderly patients with normal renal function (see **Contraindications** and **Warnings and Precautions**).

Children and adolescents

The safety and efficacy of Galvusmet have not been established in patients under 18 years of age. Galvusmet is therefore not recommended for use in paediatric patients.

Contraindications

- Hypersensitivity to the active substances or any of the excipients.
- Diabetic ketoacidosis or diabetic precoma.
- Renal impairment or renal dysfunction, defined as creatinine clearance < 60 ml/minute (see **Warnings and Precautions**)
- Acute conditions with the potential to alter renal function, such as:
  - ○ Dehydration
  - ○ Severe infection
  - ○ Shock
  - ○ Intravascular administration of iodinated contrast agents (see **Warnings and Precautions**)
- Acute or chronic disease which may cause tissue hypoxia, such as:
  - ○ Heart failure
  - ○ Respiratory failure
  - ○ Recent myocardial infarction
  - ○ Shock
- Hepatic impairment (see **Dosage and Administration**, **Warnings and Precautions** and **Adverse effects**)
- Acute alcohol intoxication, alcoholism
- Lactation (see **Pregnancy and Lactation**)

Warnings and Precautions

Galvusmet

General considerations

Galvusmet is not a substitute for insulin in patients requiring insulin. Galvusmet should not be used in patients with type 1 diabetes or in patients with ketoacidosis.

Vildagliptin

Hepatic impairment

Vildagliptin is not recommended in patients with hepatic dysfunction, including patients with pre-treatment AST or ALT > 2.5 × ULN.

Galvusmet is therefore not recommended in patients with hepatic impairment.

Liver-enzyme monitoring

There have been reports of hepatic dysfunction (including rare cases of hepatitis). In these cases, the patients were generally asymptomatic without clinical sequelae, and hepatic function test results returned to normal after discontinuation of treatment. Hepatic function tests should be performed prior to the initiation of treatment with Galvusmet in order to determine the patient's baseline values. Hepatic function should be monitored during treatment with Galvusmet at three-month intervals during the first year, and periodically thereafter. Patients who develop increased transaminase levels should be retested and, if their results are confirmed, should be monitored frequently until test results return to normal. Withdrawal of Galvusmet is recommended in patients with elevated AST or ALT levels ≥ 3 × ULN.

Patients who develop jaundice or other signs of hepatic dysfunction should discontinue treatment with Galvusmet.

Following withdrawal of treatment and normalization of hepatic function tests, treatment with Galvusmet should not be reinitiated.

Skin diseases

Skin lesions on the extremities of monkeys, such as blistering and ulceration, have been reported in non-clinical toxicology studies in association with the use of vildagliptin (see **Preclinical data**). Although no increase in the incidence of skin lesions was observed in clinical studies, experience has been limited in patients with diabetic skin complications. Therefore, monitoring for skin disorders such as blistering or ulceration – as routinely carried out in diabetic patients – is recommended.

Metformin

Lactic acidosis

Lactic acidosis is a very rare (3 cases per 100 000 patient-years), but serious, metabolic complication associated with high mortality when prompt treatment is not provided. It can occur as a result of metformin accumulation. Acute renal failure (organic or functional) may be the cause of metformin accumulation.

Cases of lactic acidosis reported thus far in association with metformin have been in patients with marked renal impairment. The incidence of lactic acidosis can and should be reduced by regular monitoring even of risk factors not associated with metformin, such as poorly controlled diabetes, ketoacidosis, prolonged fasting, excessive alcohol consumption, hepatic impairment and any hypoxic conditions.

Prior signs and symptoms are non-specific and may present as muscle cramps accompanied by gastrointestinal disorders, abdominal pain, elevated respiratory rate and pronounced asthenia. The attending physician should take note of these symptoms. The physician should also inform patients of possible signs of lactic acidosis.

Lactic acidosis is characterized by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Signs and symptoms can be recognized by the following laboratory parameters: decreased blood pH, plasma lactate levels > 5 mmol/litre, an increased anion gap and an elevated lactate/pyruvate ratio.

If lactic acidosis is suspected, metformin should be discontinued and the patient should be hospitalized immediately. It is most effective to eliminate both lactate and metformin by haemodialysis (see **Overdose**).

Renal function (see Contraindications)

Metformin is excreted via the kidneys, and creatinine clearance should therefore be monitored before initiating treatment, and regularly thereafter:

- once a year in patients with normal renal function.
- according to the physician's judgment in patients with levels at the lower limit of the normal range, or in elderly patients because asymptomatic reductions in renal function often occur in elderly patients in particular.

Particular caution is required in situations in which renal function might deteriorate owing to underlying predisposing factors or the possible use of concomitant medications (e.g. at the start of therapy with diuretics, antihypertensive agents or NSAIDs).

Iodinated contrast media

Intravascular administration of iodinated contrast media for radiological tests (i.v. urography, angiography, etc.) may lead to renal failure. Galvusmet must therefore be discontinued prior to, or at the time of, the test and must not be reinstituted until at least 48 hours afterwards, and only after renal function has been checked and found to be normal.

Surgical procedures

Galvusmet must be discontinued 48 hours before scheduled surgery with general, spinal or epidural anaesthesia. Therapy with metformin may be resumed no earlier than 48 hours after surgery, and only following resumption of oral nutrition and if renal function is normal.

Alcohol intake

Alcohol potentiates the effect of metformin on lactate metabolism. Patients should therefore be warned against excessive alcohol intake during Galvusmet therapy.

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 by discontinuation of metformin and/or by vitamin B_{12} supplementation. Measurement of haematological parameters on at least an annual basis is advised for patients receiving Galvusmet. Any disturbance that occurs should be appropriately investigated and managed.

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

Patients with type 2 diabetes previously well controlled on Galvusmet who develop laboratory abnormalities or clinical illness (especially vague or poorly defined illness) should promptly be evaluated for ketoacidosis and/or lactic acidosis. If acidosis occurs, Galvusmet must be stopped immediately and appropriate measures initiated.

Hypoglycaemia

Hypoglycaemia does not usually occur in patients receiving Galvusmet alone, but it may occur if caloric intake is deficient, if strenuous exercise is not compensated by caloric supplementation or if alcohol is consumed. 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 patients taking beta-blockers.

Loss of control of blood glucose

When a patient on antidiabetic therapy is exposed to stress such as fever, trauma, infection, surgery, etc., a temporary loss of glycaemic control may occur. In such situations, it may be necessary to withhold Galvusmet and temporarily administer insulin. Galvusmet may be reinstituted after the acute episode resolves.

Interactions

Galvusmet

There have been no formal interaction studies for Galvusmet. The following statements reflect the information available on the individual active substances.

Vildagliptin

Vildagliptin neither inhibits nor induces CYP 450 enzymes, and is therefore unlikely to interact with comedications that are metabolized by CYP 450 or that act as inhibitors or inducers of these enzymes. Drug interaction studies were conducted using 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 were observed with other oral antidiabetics (glibenclamide, pioglitazone, metformin), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin.

Metformin

Interactions which influence metformin efficacy

Reduction in hypoglycaemic efficacy

Glucocorticoids (systemic and local), beta-2-agonists, diuretics, phenothiazines (e.g. chlorpromazine), thyroid hormones, oestrogens, oral contraceptives, hormone replacement products, phenytoin, nicotinic acid, calcium channel blockers, isoniazid and tetracosactide may increase blood glucose levels.

Potentiation of hypoglycaemic efficacy

Furosemide increases plasma levels of metformin (C_{max} by 22%, AUC by 15%) with no significant change in renal clearance.
Nifedipine increases plasma levels of metformin (C_{max} by 20%, AUC by 9–20%) by increasing metformin absorption.
Cimetidine increases metformin C_{max} by 60% and AUC by 40%. The elimination half-life of metformin is unaffected. Other active substances (amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by active renal tubular secretion have the potential for interaction with metformin. Patients receiving such medicinal products should therefore be closely monitored during treatment with metformin.
ACE inhibitors may lower blood glucose.
Blood glucose may also be lowered by beta-blockers, although cardioselective (beta-1-selective) beta-blockers exhibit such interactions to a much smaller extent than do non-cardioselective agents.
Coadministration of MAO inhibitors and oral antidiabetics may improve glucose tolerance and increase the hypoglycaemic effect.
Concomitant alcohol use may potentiate the hypoglycaemic effect of metformin, and may even cause hypoglycaemic coma.

Increased or reduced hypoglycaemic effect of metformin

H_2-antagonists, clonidine and reserpine may increase or reduce the effect of metformin.
Disturbances of blood glucose control (including hyper- or hypoglycaemia) have been observed following coadministration of quinolones and metformin.

Interactions that increase the adverse effects of metformin

Diuretics

Renal dysfunction due to diuretics (especially loop diuretics) may result in lactic acidosis. Diuretics also cause blood glucose levels to rise.

Iodinated contrast media

See **Warnings and Precautions** for information on interactions with iodinated radiocontrast agents and the risk of resultant lactic acidosis.

Alcohol

Acute alcohol intoxication in patients taking metformin poses an increased risk of lactic acidosis, particularly after fasting or in the presence of malnutrition or hepatic impairment.

Interactions that influence the efficacy of other substances

Metformin lowers plasma levels of furosemide (C_{max} by 33%, AUC by 12%), and shortens the terminal half-life by 32%, without altering renal clearance of furosemide.
The effect of phenprocoumon may be reduced since its elimination is accelerated by metformin.
Interaction studies with glibenclamide, nifedipine, ibuprofen and propranolol have shown no clinically relevant effects on the pharmacokinetic parameters of these substances.

Other interactions

The warning signs of hypoglycaemia may be rendered less perceptible by the effects of sympatholytics (e.g. beta-blockers, clonidine, guanethidine, reserpine).

Pregnancy and Lactation

Pregnancy

There are no adequate data on the use of Galvusmet in pregnant women. Animal studies have shown evidence of reproductive toxicity with high doses of vildagliptin, but no evidence of reproductive toxicity with metformin. In animal studies, there was no evidence of teratogenicity with vildagliptin and metformin, but fetotoxic effects were seen at maternally toxic doses (see **Preclinical data**). The potential risk for humans is not known. Galvusmet should not be used during pregnancy.

Lactation

Animal studies have shown that both vildagliptin and metformin are excreted in the milk. It is not known whether vildagliptin passes into human milk, but small amounts of metformin are excreted in human milk. Due to the potential risk of hypoglycaemia in the neonate in connection with metformin, and due to the lack of data in humans as regards vildagliptin, Galvusmet should not be used by women who are breastfeeding (see **Contraindications**).

Effects on ability to drive and use machines

There have been no studies of the effects of this product on the ability to drive or use machines. Patients experiencing dizziness should therefore not drive or use machines.

Adverse effects

Galvusmet

No therapeutic clinical trials have been conducted with Galvusmet. However, the bioequivalence of Galvusmet with co-administered vildagliptin and metformin has been demonstrated (see **Pharmacokinetics**). 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 with vildagliptin, at a rate similar to that in the control group. A greater number of cases were reported when vildagliptin was administered in combination with an 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 hepatic function returned to normal after discontinuation of treatment.
In controlled monotherapy and add-on therapy studies of up to 24 weeks' duration, the incidence of ALT or AST elevations ≥ 3 × ULN (detected at no fewer than two consecutive measurements or at the final on-treatment visit) was 0.2% for 50 mg vildagliptin once daily, 0.3% for 50 mg vildagliptin twice daily and 0.2% for all comparators. These increases in transaminases were generally asymptomatic, not progressive and not associated with cholestasis or jaundice.
In controlled studies, hypoglycaemia was uncommon in patients receiving vildagliptin in combination with metformin and in patients receiving placebo and metformin. No severe cases of hypoglycaemia occurred in the vildagliptin group.
Gastrointestinal adverse effects, including diarrhoea and nausea, occur very commonly during the introduction of metformin.
Overall, gastrointestinal symptoms were reported in 12.9% of patients treated with the combination of vildagliptin and metformin, compared with 18.1% of patients treated with metformin alone.
In comparative controlled monotherapy studies, hypoglycaemia was uncommon.

Adverse effects, reported in double-blind studies in patients who received vildagliptin as monotherapy and add-on therapy, are listed below (see table 1) by system organ class and absolute frequency:
Frequencies are defined as: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10 000 to < 1/1000), very rare (< 1/10 000), not known (cannot be estimated based on available data). Within each frequency grouping, adverse effects are listed in the order of decreasing seriousness.

Table 1:
Infections
Very rare: Upper respiratory tract infections, nasopharyngitis.

Endocrine disorders
Not known: Pancreatitis.

Nervous system disorders
Common: Dizziness, tremor.
Uncommon: Headache.

Vascular disorders
Uncommon: Peripheral oedema.

Gastrointestinal disorders
Common: Nausea.
Uncommon: Diarrhoea, constipation.

Hepatic disorders
Rare: Elevated transaminase levels.

Musculoskeletal disorders
Uncommon: Arthralgia.

Metabolism disorders
Uncommon: Hypoglycaemia, weight gain.

General disorders
Uncommon: Asthenia.
None of the adverse effects reported with vildagliptin monotherapy were observed at clinically significantly higher rates when vildagliptin was administered concomitantly with metformin.

Metformin
The known adverse effects of metformin are summarized in table 2.

Table 2:
Blood and lymphatic system disorders
Isolated cases of leukopenia, thrombocytopenia and haemolytic anaemia.
Very rare: Reduced vitamin B_{12} blood levels.

Metabolism and nutrition disorders
Very rare: Lactic acidosis (incidence: 3 cases per 100 000 patient-years; see **Warnings and Precautions**).

Nervous system disorders
Common: Metallic taste (3%).
Uncommon: Fatigue.

Gastrointestinal disorders
Common to very common: Gastrointestinal disorders (5–15%) such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite.
These symptoms usually occur at the start of treatment and resolve spontaneously in most cases.

Hepatobiliary disorders
Isolated cases: Abnormal results in hepatic function tests, e.g. elevated transaminases or hepatitis (reversible after discontinuing metformin).

Skin and subcutaneous tissue disorders
Very rare: Skin reactions such as erythema, pruritus, urticaria.

Overdose

Signs and symptoms

Vildagliptin
Oedema and muscle pain were dose-limited in clinical studies. At 600 mg, one subject experienced oedema of the hands and feet, and an excessive increase in creatine phosphokinase (CPK) levels, accompanied by elevated levels of aspartate aminotransferase (AST), C-reactive protein and myoglobin. Three additional subjects in this dosage group presented with oedema of both feet, accompanied by paraesthesia in two cases. All symptoms and laboratory abnormalities resolved after study-drug discontinuation.
In case of overdosage, the medicinal product should be withdrawn and the patient should be given symptomatic and supportive treatment.
Vildagliptin is not dialysable; the major hydrolysis metabolite can be removed by haemodialysis.

Metformin
Hypoglycaemia has not been seen even after extremely high metformin doses (up to 85 g), but lactic acidosis has occurred under such circumstances. Lactic acidosis is a medical emergency necessitating hospitalization (see **Warnings and Precautions**). Both lactate and metformin are removed by haemodialysis.

Properties and Actions

ATC code: A10BD08

Mechanism of action / Pharmacodynamics

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

Vildagliptin
Administration of vildagliptin inhibits DPP-4 activity, thereby increasing 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 50–100 mg vildagliptin daily in patients with type 2 diabetes significantly improved markers of beta cell function, including HOMA-β (Homeostasis Model Assessment–β), proinsulin to insulin ratio and measures of beta cell responsiveness from the frequently employed meal tolerance test. In non-diabetic (normoglycaemic) 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 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 delaying gastric emptying is not observed with vildagliptin treatment.

Metformin
Metformin is an oral antidiabetic agent of the biguanide class, whose hypoglycaemic effect is based primarily on the overcoming of insulin resistance in liver and muscle. In the presence of insulin, it lowers both basal and postprandial plasma glucose levels. Metformin does not stimulate insulin secretion and, when used alone, does not produce hypoglycaemia. The hypoglycaemic effect is based on three mechanisms:

In the liver
Hepatic glucose production is largely responsible for hyperglycaemia in the fasting state. Metformin reduces hepatic glucose production activated by insulin resistance by inhibiting gluconeogenesis and glycogenolysis, thereby at the same time counteracting the hyperglycaemic effect of glucagon. By this mechanism, metformin reduces fasting hyperglycaemia.

In muscle
Impaired peripheral glucose uptake and storage are mainly responsible for postprandial hyperglycaemia. Metformin increases cellular sensitivity to insulin by stimulating insulin-receptor tyrosine kinase activity, thereby promoting cellular glucose uptake. Metformin increases the capacity of all cell-membrane glucose transporters (GLUTs). This effect of metformin is particularly marked in hyperglycaemic states. Intracellular glycogen synthesis is increased by stimulation of the key enzyme, glycogen synthase. By this mechanism, metformin reduces postprandial hyperglycaemia.

In the intestine
Metformin delays intestinal glucose absorption, thereby reducing postprandial glucose exposure.

Effects on lipid metabolism and fibrinolysis
Metformin also has a positive effect on human lipid metabolism, independently of its effect on blood glucose. Medium- and long-term controlled clinical studies have demonstrated that therapeutic doses of metformin reduce total cholesterol, LDL cholesterol and triglyceride levels. In addition, metformin was shown in some studies to increase HDL cholesterol levels.
Metformin also possesses fibrinolytic properties.

Clinical efficacy

Galvusmet
There have been no studies of the clinical efficacy of Galvusmet. The safety and efficacy of the separate components have already been established. Co-administration of the two components has been evaluated for safety and efficacy in two clinical studies. Both of these studies demonstrated an added benefit for vildagliptin in patients with inadequately controlled type 2 diabetes who had been treated with metformin.
In a 24 week, double-blind, placebo-controlled study in patients with type 2 diabetes whose glycaemia was inadequately controlled on metformin alone at doses ≥ 2000 mg, vildagliptin combined with metformin showed a statistically significantly greater reduction in HbA_{1c} than that achieved in the group using metformin and placebo (the mean difference was -0.7% in the group using 50 mg vildagliptin once daily and -1.1% in the group using 50 mg vildagliptin twice daily).
The efficacy of vildagliptin in combination with 1000 mg metformin was evaluated in another double-blind, placebo-controlled clinical study of 52 weeks' total duration (12 week core study [n = 132] plus a 40 week extension [n = 71]). The addition of vildagliptin (50 mg once daily) to metformin resulted in an additional and statistically significant reduction in mean HbA_{1c} from baseline (0.55%), compared with the group using metformin plus placebo (+0.1%), at the end of the first 12 weeks of the study (mean baseline HbA_{1c} of 7.7% and 7.9%, respectively). At 52 weeks, the mean change from baseline HbA_{1c} was statistically significantly greater and more marked in the group using vildagliptin (50 mg) plus metformin than in the group on metformin alone (between group difference of -1.1%).

In a 24 week study in patients whose blood glucose was inadequately controlled with metformin, twice daily 50 mg doses of vildagliptin were compared with once daily 30 mg doses of pioglitazone. Mean reductions from the 8.4% baseline HbA1c were 0.9% with vildagliptin added to metformin and 1.0% with pioglitazone added to metformin. Reductions were larger in both treatment groups, i.e. 1.5%, for baseline HbA1c > 9.0%. Patients receiving pioglitazone in addition to metformin gained 1.9 kg, while those receiving vildagliptin in addition to metformin gained 0.3 kg. In a long-term study lasting up to two years, twice daily 50 mg doses of vildagliptin were compared with once daily doses of up to 6 mg glimepiride in patients treated with metformin. After 2 years, mean reductions in HbA1c were 0.06% with the combination of vildagliptin / metformin and 0.14% with glimepiride / metformin. The change in body weight was -0.2 kg with vildagliptin and +1.2 kg with glimepiride. The incidence of hypoglycaemic episodes was significantly lower in the vildagliptin group (2.3%) than in the glimepiride group (18.2%).

Vildagliptin

Two 24 week, double-blind, placebo-controlled studies were carried out in treatment-naive patients with type 2 diabetes. In these studies, administration of 50 mg vildagliptin once daily resulted in mean changes from baseline in HbA$_{1c}$ (-0.8% and -0.5%, respectively) that were statistically significant compared with placebo.

In addition, vildagliptin monotherapy was compared with metformin, rosiglitazone or pioglitazone in several studies in treatment-naive patients. The patients had had diabetes for an average of two years. In these studies, vildagliptin showed a clinically relevant reduction in HbA$_{1c}$ as compared with baseline. Non-inferiority was statistically demonstrated as compared with rosiglitazone, but not as compared with metformin and pioglitazone.

In a two-year long-term study, 50 mg vildagliptin twice daily was compared with daily doses of up to 320 mg gliclazide. After 2 years, mean reductions in HbA1c were 0.5% with vildagliptin and 0.6% with gliclazide. There was less weight gain with vildagliptin (0.75 kg) and fewer hypoglycaemic episodes (0.7%) than with gliclazide (1.6 kg and 1.7%, respectively).

The studies of combinations with metformin are described above.

Metformin

The prospective, randomized UKPDS study (UK Prospective Diabetes Study) has established the long-term benefit of intensive glycaemic control in patients with type 2 diabetes. Analysis of the results for overweight patients – treated with metformin after failure of diet alone – showed:

- a significant reduction in the absolute risk of diabetes-related complications in the metformin group (29.8 events / 1000 patient-years) vs. both diet alone (43.3 events / 1000 patient-years), p = 0.0023, and the combined sulphonylurea and insulin monotherapy groups (40.1 events / 1000 patient-years), p = 0.0034
- a significant reduction in the absolute risk of diabetes-related mortality: 7.5 events / 1000 patient-years with metformin, 12.7 events / 1000 patient-years on diet alone (p = 0.017)
- a significant reduction in the absolute risk of overall mortality: 13.5 events / 1000 patient-years with metformin vs. 20.6 events / 1000 patient-years on diet alone (p = 0.011) and 18.9 events / 1000 patient-years for the combined sulphonylurea and insulin monotherapy groups (p = 0.021)
- a significant reduction in the absolute risk of myocardial infarction: 11 events / 1000 patient-years with metformin vs. 18 events / 1000 patient-years on diet alone (p = 0.01)

Pharmacokinetics

Absorption

Galvusmet

In the bioequivalence studies of Galvusmet at three dosage strengths (50 mg / 500 mg, 50 mg / 850 mg and 50 mg / 1000 mg) vs. free combination of vildagliptin and metformin at the corresponding doses, the bioavailability of both vildagliptin and metformin were shown to be unchanged.

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

Vildagliptin

Vildagliptin is rapidly absorbed, with an oral bioavailability of 85%. Peak plasma concentrations are attained after about 1 hour. Absorption is not affected to a relevant extent by ingestion of food. Food does not alter overall exposure (AUC).

Metformin

Following oral administration, T_{max} is 2.5 hours, and absorption is complete after 6 hours. Absorption is assumed to take place primarily in the upper gastrointestinal tract. The absolute bioavailability of a 500 mg or 850 mg dose is approximately 50-60% in healthy subjects. Ingestion of a single oral dose of 500–2500 mg was followed by a less than proportional increase in C_{max}, possibly due to a saturable mechanism. Using standard metformin dosages, steady-state plasma levels are reached within 24–48 hours. These are generally lower than 1 µg/ml. In controlled clinical studies, C_{max} was not found to exceed 4 µg/ml, even at maximum doses.

Food decreases and delays the absorption of metformin. Following ingestion of an 850 mg dose with food, a 40% lower C_{max}, 25% decrease in AUC and 35 minute prolongation of T_{max} were observed. The clinical relevance of these findings is thus far 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.

Metformin

Plasma protein binding of metformin is negligible. Metformin diffuses to some extent into erythrocytes. Peak blood levels are lower than the peak plasma levels and are achieved at approximately the same time. The red blood cells probably represent a secondary compartment of distribution.

The mean volume of distribution is 63–276 litres.

It is not known whether metformin crosses the placenta or is excreted in breast milk. In rats, small amounts pass into the milk.

Metabolism

Vildagliptin

Vildagliptin is largely metabolized (69% of the dose), to some extent by DPP-4. The major metabolite, LAY151 (57% of the dose), which is formed by hydrolysis, is inactive. There is also an amide hydrolysis product (4% of the dose). Vildagliptin is not metabolized by cytochrome P450 enzymes.

Metformin

Metformin is not metabolized in humans.

Elimination

Vildagliptin

85% of the dose is excreted in the urine and 15% of the dose is recovered in the faeces. Unchanged vildagliptin accounts for 23% of the dose. The elimination half-life is about 3 hours.

Metformin

Metformin is excreted unchanged in the urine. Renal clearance is > 400 ml/minute, and hence some 3.5 times greater than creatinine clearance. The drug is thus chiefly eliminated by active tubular secretion. The plasma elimination half-life after oral dosing is about 6.5 hours. When measured in whole blood, the half-life is approximately 17.6 hours.

In subjects with normal renal function, metformin does not accumulate in the body at the standard dosage (1500–2000 mg).

Pharmacokinetics in special patient populations

Sex

Vildagliptin

No differences have been reported between the pharmacokinetics of vildagliptin in men and those in women.

Elderly patients

Vildagliptin

Plasma levels are elevated in patients over 70 years of age. However, the change in exposure to vildagliptin is not clinically relevant.

Impaired hepatic function

Vildagliptin

Exposure to vildagliptin (100 mg) was not elevated after a single dose of 100 mg in patients with mild and moderate hepatic impairment; it was elevated by 22% (68% upper confidence limit) in patients with severe hepatic impairment.

Impaired renal function

Vildagliptin

Systemic exposure to vildagliptin was elevated both in patients with mild, moderate, or severe renal impairment, and in ESRD patients on haemodialysis; it was elevated by 58% in patients with severe renal impairment (102% upper confidence limit).

Metformin

In patients with renal impairment, renal clearance decreases in proportion to creatinine clearance, with the elimination half-life prolonged and a risk of accumulation.

Preclinical data

Animal studies of up to 13 weeks have been conducted with the combined active substances of Galvusmet. No new toxicities associated with the combination were identified. The following data are findings from studies performed with vildagliptin or metformin individually.

Vildagliptin

In a distribution study in rats, concentrations measured in kidney and liver tissue were 10-30 times higher than concentrations in the plasma.

An inhibitory action on cardiac sodium channels, a decreased rate of depolarization in Purkinje fibres, slowed conduction in isolated rabbit hearts and a widening of the QRS complex in the ECG of dogs were observed at *in vitro* concentrations and dog *in vivo* plasma concentrations that were markedly higher (80–260 times higher in the *in vitro* findings and 43 times higher in the *in vivo* findings) than

C_{max}-based exposure levels in humans given 50 mg vildagliptin.

A two-year carcinogenicity study was conducted in rats given oral doses of up to 900 mg/kg (approximately 370 times AUC exposure in humans given 50 mg). No increases in tumour incidence attributable to vildagliptin were observed. A two-year carcinogenicity study was conducted in mice given oral doses of up to 1000 mg/kg (up to 420 times AUC exposure in humans given a dose of 50 mg). The incidence of mammary tumours was elevated in female mice given approximately 260 times the human dose of 50 mg vildagliptin; mammary tumours were not more frequent at approximately 100 times human exposure levels. The incidence of haemangiosarcoma increased in male mice at AUC exposure levels ≥ 74 times those associated with the human dose of 50 mg vildagliptin, and in female mice at exposure levels about 260 times those in humans. No significant increase in the incidence of haemangiosarcoma was observed in males at vildagliptin exposure levels approximately 27 times those in humans, or in females at exposure levels approximately 100 times those in humans.

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 at up to 2000 mg/kg, or approximately 2000 times the human dose. An *in vivo* mouse liver comet assay using the same dose was also negative.

In a 13 week toxicity study in cynomolgus monkeys, skin lesions were recorded at doses ≥ 5 mg/kg/day. These lesions were confined to the extremities (hands, feet, ears and tail).

At 5 mg/kg/day (AUC-based exposure slightly higher than human exposure following a 50 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 above 20 mg/kg/day (approximately 5 times the human AUC exposure at the 50 mg dose).

Necrotic lesions of the tail were observed at ≥ 80 mg/kg/day.

Skin lesions were reversible (up to at least 80 mg/kg) if treatment was stopped before necrosis occurred. Skin lesions have not been observed in humans or in other species treated with vildagliptin.

Metformin

Preclinical study data have yielded no evidence of special risks for human use, based on studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenicity and reproductive toxicity.

Reproductive toxicity

Metformin has no effect on fertility, is not teratogenic and does not influence neonatal development.

Mutagenicity

All study results (Ames test, gene mutation test, chromosome aberration test, micronucleus test) have shown that metformin has no mutagenic or clastogenic effects.

Carcinogenicity

Metformin is not carcinogenic in rodents given doses of up to 900 mg/kg/day (rats) and 1500 mg/kg/day (mice).

Other information

Shelf-life

See folding box

Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage

See folding box

Pack sizes

Country specific pack sizes

Manufacturer

See folding box

Information last revised

August 2010

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30 September 2010

® = registered trademark

Novartis Pharma AG, Basle, Switzerland

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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