

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 $\leq$ 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 $> 2.5 \times \text{ULN}$ (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 $> 2.5 \times \text{ULN}$. 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 $\geq 3 \times \text{ULN}$. 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**).

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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
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Vitamin B₁₂ levels
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Change in the clinical status of patients with previously controlled type 2 diabetes
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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.

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