

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 and 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 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:
 - o Dehydration
 - o Severe infection
 - o Shock
 - o Intravascular administration of iodinated contrast agents (see **Warnings and Precautions**)

Acute or chronic disease which may cause tissue hypoxia, such as:

- o Heart failure
- o Respiratory failure
- o Recent myocardial infarction
- o 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 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 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.

Alcohol intake

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

Vitamin B₁₂ levels

Metformin has been associated with a decrease in serum vitamin B₁₂ 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 B₁₂ 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.

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.e. 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 reinitiated 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.

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