

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use JANUMET safely and effectively. See full prescribing information for JANUMET.

JANUMET® (sitagliptin and metformin hydrochloride) tablets, for oral use

Initial U.S. Approval: 2007

WARNING: LACTIC ACIDOSIS

See full prescribing information for complete boxed warning.

- Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio, and metformin plasma levels generally >5 mcg/mL. (5.1)
- Risk factors include renal impairment, concomitant use of certain drugs, age ≥65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the Full Prescribing Information. (5.1)
- If lactic acidosis is suspected, discontinue JANUMET and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.1)

INDICATIONS AND USAGE

JANUMET is a combination of sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin hydrochloride (HCl), a biguanide, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)

Limitations of Use:

- JANUMET should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. (1)
- JANUMET has not been studied in patients with a history of pancreatitis. (1, 5.2)

DOSAGE AND ADMINISTRATION

- Individualize the starting dose of JANUMET based on the patient's current regimen. (2.1)
- Adjust the dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 100 mg sitagliptin and 2000 mg metformin. (2.1)
- Give twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal effects due to metformin. (2.1)
- Prior to initiation, assess renal function with estimated glomerular filtration rate (eGFR) (2.2)
 - Do not use in patients with eGFR below 30 mL/min/1.73 m².
 - JANUMET is not recommended in patients with eGFR between 30 and less than 45 mL/min/1.73 m².
- JANUMET may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures. (2.3)

DOSAGE FORMS AND STRENGTHS

Tablets: 50 mg sitagliptin/500 mg metformin HCl and 50 mg sitagliptin/1000 mg metformin HCl (3)

CONTRAINDICATIONS

- Severe renal impairment: (eGFR below 30 mL/min/1.73 m²) (4)
- Metabolic acidosis, including diabetic ketoacidosis. (4)
- History of a serious hypersensitivity reaction to JANUMET, sitagliptin, or metformin, such as anaphylaxis or angioedema. (5.9, 6.2)

WARNINGS AND PRECAUTIONS

- Lactic acidosis: See boxed warning. (5.1)
- There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. If pancreatitis is suspected, promptly discontinue JANUMET. (5.2)
- Heart failure has been observed with two other members of the

patients who have known risk factors for heart failure. Monitor patients for signs and symptoms. (5.3)

- There have been postmarketing reports of acute renal failure, sometimes requiring dialysis. Before initiating JANUMET and at least annually thereafter, assess renal function. (5.4)
- Vitamin B₁₂ deficiency: Metformin may lower vitamin B₁₂ levels. Measure hematologic parameters annually. (5.5)
- When used with an insulin secretagogue (e.g., sulfonylurea) or with insulin, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia. (5.7)
- There have been postmarketing reports of serious allergic and hypersensitivity reactions in patients treated with sitagliptin (one of the components of JANUMET), such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. In such cases, promptly stop JANUMET, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes. (5.9)
- Severe and disabling arthralgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue drug if appropriate. (5.10)
- There have been postmarketing reports of bullous pemphigoid requiring hospitalization in patients taking DPP-4 inhibitors. Tell patients to report development of blisters or erosions. If bullous pemphigoid is suspected, discontinue JANUMET. (5.11)
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with JANUMET. (5.12)

ADVERSE REACTIONS

- The most common adverse reactions reported in ≥5% of patients simultaneously started on sitagliptin and metformin and more commonly than in patients treated with placebo were diarrhea, upper respiratory tract infection, and headache. (6.1)
- Adverse reactions reported in ≥5% of patients treated with sitagliptin in combination with sulfonylurea and metformin and more commonly than in patients treated with placebo in combination with sulfonylurea and metformin were hypoglycemia and headache. (6.1)
- Hypoglycemia was the only adverse reaction reported in ≥5% of patients treated with sitagliptin in combination with insulin and metformin and more commonly than in patients treated with placebo in combination with insulin and metformin. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Carbonic anhydrase inhibitors may increase risk of lactic acidosis. Consider more frequent monitoring. (7.1)
- Drugs that reduce metformin clearance (such as ranolazine, vandetanib, dolutegravir, and cimetidine) may increase the accumulation of metformin. Consider the benefits and risks of concomitant use. (7.2)
- Alcohol can potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake. (7.3)

USE IN SPECIFIC POPULATIONS

- There are no adequate and well-controlled studies in pregnant women. To report drug exposure during pregnancy call 1-800-986-8999. (8.1)
- Geriatric Use: Assess renal function more frequently. (8.5)
- Hepatic Impairment: Avoid use in patients with hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS

Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio, and metformin plasma levels generally >5 mcg/mL [see *Warnings and Precautions (5.1)*].

Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.

Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high risk groups are provided in the full prescribing information [see *Dosage and Administration (2.2)*, *Contraindications (4)*, *Warnings and Precautions (5.1)*, *Drug Interactions (7)*, and *Use in Specific Populations (8.6, 8.7)*].

If metformin-associated lactic acidosis is suspected, immediately discontinue JANUMET and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended [see *Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

JANUMET is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Limitations of Use

JANUMET should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

JANUMET has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using JANUMET. [See *Warnings and Precautions (5.2)*.]

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The dosage of JANUMET should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 100 mg sitagliptin and 2000 mg metformin hydrochloride (HCl). Initial combination therapy or maintenance of combination therapy should be individualized and left to the discretion of the health care provider.

JANUMET should generally be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects due to metformin. JANUMET must not be split or divided before swallowing.

The starting dose of JANUMET should be based on the patient's current regimen. JANUMET should be given twice daily with meals. The following doses are available:

50 mg sitagliptin/500 mg metformin HCl

50 mg sitagliptin/1000 mg metformin HCl.

The recommended starting dose in patients not currently treated with metformin is 50 mg sitagliptin/500 mg metformin HCl twice daily, with gradual dose escalation recommended to reduce gastrointestinal side effects associated with metformin.

The starting dose in patients already treated with metformin should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and the dose of metformin already being taken. For patients taking metformin 850 mg twice daily, the recommended starting dose of JANUMET is 50 mg sitagliptin/1000 mg metformin HCl twice daily.

No studies have been performed specifically examining the safety and efficacy of JANUMET in patients previously treated with other oral antihyperglycemic agents and switched to JANUMET. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur.

2.2 Recommendations for Use in Renal Impairment

Assess renal function prior to initiation of JANUMET and periodically thereafter.

JANUMET is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m² [see *Contraindications (4) and Warnings and Precautions (5.1)*].

JANUMET is not recommended in patients with an eGFR between 30 and less than 45 mL/min/1.73 m² because these patients require a lower dosage of sitagliptin than what is available in the fixed combination JANUMET product.

2.3 Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue JANUMET at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m²; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart JANUMET if renal function is stable [see *Warnings and Precautions (5.1)*].

3 DOSAGE FORMS AND STRENGTHS

Tablets:

- 50 mg/500 mg tablets are light pink, capsule-shaped, film-coated tablets with “575” debossed on one side.
- 50 mg/1000 mg tablets are red, capsule-shaped, film-coated tablets with “577” debossed on one side.

4 CONTRAINDICATIONS

JANUMET is contraindicated in patients with:

- Severe renal impairment (eGFR below 30 mL/min/1.73 m²) [see *Warnings and Precautions (5.1)*].
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
- History of a serious hypersensitivity reaction to JANUMET, sitagliptin, or metformin, such as anaphylaxis or angioedema. [See *Warnings and Precautions (5.9)*; *Adverse Reactions (6.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

There have been postmarketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant bradyarrhythmias have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate/pyruvate ratio; metformin plasma levels were generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of JANUMET. In JANUMET-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin HCl is dialyzable, with a clearance of up to 170 mL/min under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue JANUMET and report these symptoms to their health care provider.

For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:

Renal Impairment

The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include [see *Dosage and Administration* (2.2), *Clinical Pharmacology* (12.3)]:

- Before initiating JANUMET, obtain an estimated glomerular filtration rate (eGFR).
- JANUMET is contraindicated in patients with an eGFR below 30 mL/min/1.73 m² [see *Contraindications* (4)].
- JANUMET is not recommended in patients with an eGFR between 30 and less than 45 mL/min/1.73 m² because these patients require a lower dosage of sitagliptin than what is available in the fixed combination JANUMET product.
- Obtain an eGFR at least annually in all patients taking JANUMET. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

Drug Interactions

The concomitant use of JANUMET with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation [see *Drug Interactions* (7)]. Therefore, consider more frequent monitoring of patients.

Age 65 or Greater

The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients [see *Use in Specific Populations* (8.5)].

Radiological Studies with Contrast

Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop JANUMET at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m²; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart JANUMET if renal function is stable.

Surgery and Other Procedures

Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. JANUMET should be temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic States

Several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue JANUMET.

Excessive Alcohol Intake

Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving JANUMET.

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