CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-044

LABELING

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/metformin HCl) tablets
Initial U.S. Approval: 2007

WARNING: LACTIC ACIDOSIS
See full prescribing information for complete boxed warning.

- **Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure. (5.1)**
- **Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate. (5.1)**
- **If acidosis is suspected, discontinue JANUMET and hospitalize the patient immediately. (5.1)**

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	2/2008
Dosage and Administration	
Recommended Dosing (2.1)	2/2008
Contraindications (4)	1/2008
Warnings and Precautions	
Use with Medications Known to Cause Hypoglycemia (5.8)	2/2008
Hypersensitivity Reactions (5.13)	1/2008
Macrovascular Outcomes (5.14)	2/2008

----------INDICATIONS AND USAGE----------

JANUMET is a dipeptidyl peptidase-4 (DPP-4) inhibitor and biguanide combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both sitagliptin and metformin is appropriate. (1)

Important 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 combination with insulin. (1)

----------DOSAGE AND ADMINISTRATION----------

- Individualize the starting dose of JANUMET based on the patient's current regimen. (2.1)
- May 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)
- JANUMET should be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects due to metformin. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

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

----------CONTRAINDICATIONS----------

- Renal dysfunction, e.g., serum creatinine ≥1.5 mg/dL [males], ≥1.4 mg/dL [females] or abnormal creatinine clearance. (4, 5.1, 5.3)
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. (4, 5.1)
- History of a serious hypersensitivity reaction to JANUMET or sitagliptin (one of the components of JANUMET), such as anaphylaxis or angioedema. (5.13, 6.2)
- Temporarily discontinue JANUMET in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials. (4, 5.1, 5.10)

----------WARNINGS AND PRECAUTIONS----------

- Do not use JANUMET in patients with hepatic disease. (5.1, 5.2)
- Before initiating JANUMET and at least annually thereafter, assess renal function and verify as normal. (4, 5.1, 5.3, 5.9)
- Measure hematologic parameters annually. (5.4, 6.1)
- Warn patients against excessive alcohol intake. (5.1, 5.5)
- May need to discontinue JANUMET and temporarily use insulin during periods of stress and decreased intake of fluids and food as may occur with fever, trauma, infection or surgery. (5.6, 5.7, 5.11, 5.12)
- Promptly evaluate patients previously controlled on JANUMET who develop laboratory abnormalities or clinical illness for evidence of ketoacidosis or lactic acidosis. (5.1, 5.7, 5.11, 5.12)
- When used with an insulin secretagogue (e.g., sulfonylurea, meglitinide), a lower dose of the insulin secretagogue may be required to reduce the risk of hypoglycemia. (2.1, 5.8)
- 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. (5.13, 6.2)
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with JANUMET or any other oral anti-diabetic drug (5.14).

---------- 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)
- Nasopharyngitis was the only adverse reaction reported in ≥5% of patients treated with sitagliptin monotherapy and more commonly than in patients given placebo. (6.1)
- The most common (>5%) adverse reactions due to initiation of metformin therapy are diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache. (6.1)

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

----------DRUG INTERACTIONS----------

- Cationic drugs eliminated by renal tubular secretion: Use with caution. (5.9, 7.1)

---------- USE IN SPECIFIC POPULATIONS ----------

- Safety and effectiveness of JANUMET in children under 18 years have not been established. (8.4)
- There are no adequate and well-controlled studies in pregnant women. To report drug exposure during pregnancy call 1-800-986-8999. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 2/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: LACTIC ACIDOSIS

Lactic acidosis is a rare, but serious complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic insufficiency, renal impairment, and acute congestive heart failure.

The onset is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress.

Laboratory abnormalities include low pH, increased anion gap and elevated blood lactate.

If acidosis is suspected, JANUMET[1] should be discontinued and the patient hospitalized immediately. *[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 when treatment with both sitagliptin and metformin is appropriate. *[See Clinical Studies (14).]*

Important Limitations of Use

JANUMET should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

JANUMET has not been studied in combination with insulin.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The dosage of antihyperglycemic therapy with 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. 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.

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 hydrochloride

50 mg sitagliptin/1000 mg metformin hydrochloride.

Patients inadequately controlled with diet and exercise alone

If therapy with a combination tablet containing sitagliptin and metformin is considered appropriate for a patient with type 2 diabetes mellitus inadequately controlled with diet and exercise alone, the recommended starting dose is 50 mg sitagliptin/500 mg metformin hydrochloride twice daily. Patients with inadequate glycemic control on this dose can be titrated up to 50 mg sitagliptin/1000 mg metformin hydrochloride twice daily.

Patients inadequately controlled on metformin monotherapy

If therapy with a combination tablet containing sitagliptin and metformin is considered appropriate for a patient inadequately controlled on metformin alone, the recommended starting dose of JANUMET 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 hydrochloride twice daily.

Patients inadequately controlled on sitagliptin monotherapy

If therapy with a combination tablet containing sitagliptin and metformin is considered appropriate for a patient inadequately controlled on sitagliptin alone, the recommended starting dose of JANUMET is 50 mg sitagliptin/500 mg metformin hydrochloride twice daily. Patients with inadequate control on this dose can be titrated up to 50 mg sitagliptin/1000 mg metformin hydrochloride twice daily. Patients taking sitagliptin monotherapy dose-adjusted for renal insufficiency should not be switched to JANUMET *[see Contraindications (4)]*.

Patients switching from co-administration of sitagliptin and metformin

For patients switching from sitagliptin co-administrated with metformin, JANUMET may be initiated at the dose of sitagliptin and metformin already being taken.

Patients inadequately controlled on dual combination therapy with any two of the following antihyperglycemic agents: sitagliptin, metformin or a sulfonylurea

If therapy with a combination tablet containing sitagliptin and metformin is considered appropriate in this setting, the usual starting dose of JANUMET should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose). In determining the starting dose of the metformin component, the patient's level of glycemic control and current dose (if any) of metformin should be considered. Gradual dose escalation to reduce the gastrointestinal (GI) side effects associated with metformin should be considered. Patients currently on or initiating a sulfonylurea may require lower sulfonylurea doses to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.9)]*.

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.

3 DOSAGE FORMS AND STRENGTHS

- 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 (sitagliptin/metformin HCl) is contraindicated in patients with:

- Renal disease or renal dysfunction, e.g., as suggested by serum creatinine levels ≥1.5 mg/dL [males], ≥1.4 mg/dL [females] or abnormal creatinine clearance which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia *[see Warnings and Precautions (5.1)]*.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.

- History of a serious hypersensitivity reaction to JANUMET or sitagliptin (one of the components of JANUMET), such as anaphylaxis or angioedema. *[See Warnings and Precautions (5.13) and Adverse Reactions (6.2).]*

JANUMET 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 Warnings and Precautions (5.10)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

Metformin hydrochloride

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with JANUMET; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking metformin, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure *[see Warnings and Precautions (5.3, 5.5, 5.6, 5.10)]*.

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur *[see Warnings and Precautions (5.11)]*. Metformin should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking metformin do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling *[see Warnings and Precautions (5.7, 5.12)]*.

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

DOCKET ALARM

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