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

JANUMET® XR (sitagliptin and metformin HCl extended-release) tablets
Initial U.S. Approval: 2012

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 XR and hospitalize the patient immediately. (5.1)**

----------RECENT MAJOR CHANGES----------
Dosage and Administration
Recommended Dosing (2.1) 02/2013

----------INDICATIONS AND USAGE----------
JANUMET XR 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 extended-release is appropriate. (1, 14)

Important Limitations of Use:
- Not for the treatment of type 1 diabetes or diabetic ketoacidosis. (1)
- Has not been studied in patients with a history of pancreatitis. (1, 5.2)

---------- DOSAGE AND ADMINISTRATION----------
- Individualize the starting dose of JANUMET XR 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 extended-release. (2.1)
- Administer once daily with a meal preferably in the evening. Gradually escalate the dose to reduce the gastrointestinal side effects due to metformin. (2.1)
- Maintain the same total daily dose of sitagliptin and metformin when changing between JANUMET and JANUMET XR, without exceeding the maximum recommended daily dose of 2000 mg metformin extended-release. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
JANUMET XR Tablets: 100 mg sitagliptin/1000 mg metformin HCl extended-release, 50 mg sitagliptin/500 mg metformin HCl extended-release, and 50 mg sitagliptin/1000 mg metformin HCl extended-release. (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, 5.4)
- Metabolic acidosis, including diabetic ketoacidosis. (4, 5.1)
- History of a serious hypersensitivity reaction (e.g., anaphylaxis or angioedema) to JANUMET XR or to one of its components. (5.14, 6.2)

----------WARNINGS AND PRECAUTIONS----------
- Lactic acidosis: Warn against excessive alcohol intake. JANUMET XR is not recommended in hepatic impairment and is contraindicated in renal impairment. Ensure normal renal function before initiating and at least annually thereafter.
- Temporarily discontinue JANUMET XR in patients undergoing radiologic studies with intravascular administration of iodinated contrast materials or any surgical procedures necessitating restricted intake of food or fluids. (5.1, 5.3, 5.4, 5.7)
- There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis in patients treated with sitagliptin (one of the components of JANUMET XR) with or without metformin. If pancreatitis is suspected, promptly discontinue JANUMET XR. (5.2)
- There have been postmarketing reports of acute renal failure in patients treated with sitagliptin with or without metformin, sometimes requiring dialysis. Before initiating JANUMET XR and at least annually thereafter, assess renal function and verify as normal. (4, 5.1, 5.4, 5.10, 6.2)
- Vitamin B_{12} deficiency: Metformin may lower Vitamin B_{12} levels. Measure hematologic parameters annually. (5.5, 6.1)
- 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 minimize the risk of hypoglycemia. (2.1, 5.9)
- There have been postmarketing reports of serious allergic and hypersensitivity reactions in patients treated with sitagliptin, such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. In such cases, promptly stop JANUMET XR, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes. (5.14, 6.2)
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with JANUMET XR or any other anti-diabetic drug. (5.15)

---------- 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----------
- Cationic drugs eliminated by renal tubular secretion: Use with caution. (5.10, 7.2)

---------- USE IN SPECIFIC POPULATIONS ----------
- Safety and effectiveness of JANUMET XR 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 Medication Guide.

Revised: 02/2013

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 impairment, renal impairment, and acute congestive heart failure.

The onset of lactic acidosis 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 XR (sitagliptin and metformin HCl extended-release) tablets should be discontinued and the patient hospitalized immediately. *[See Warnings and Precautions (5.1).]*

1 INDICATIONS AND USAGE

JANUMET® XR 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 extended-release is appropriate. *[See Clinical Studies (14).]*

Important Limitations of Use

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

JANUMET XR 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 XR. *[See Warnings and Precautions (5.2).]*

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The dose of JANUMET XR 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.

- In patients not currently treated with metformin, the recommended total daily starting dose of JANUMET XR is 100 mg sitagliptin and 1000 mg metformin hydrochloride (HCl) extended-release. Patients with inadequate glycemic control on this dose of metformin can be titrated gradually, to reduce gastrointestinal side effects associated with metformin, up to the maximum recommended daily dose.
- In patients already treated with metformin, the recommended total daily starting dose of JANUMET XR is 100 mg sitagliptin and the previously prescribed dose of metformin.
- For patients taking metformin immediate-release 850 mg twice daily or 1000 mg twice daily, the recommended starting dose of JANUMET XR is two 50 mg sitagliptin/1000 mg metformin hydrochloride extended-release tablets taken together once daily.
- Maintain the same total daily dose of sitagliptin and metformin when changing between JANUMET (sitagliptin and metformin HCl immediate-release) and JANUMET XR. Patients with inadequate glycemic control on this dose of metformin can be titrated gradually, to reduce gastrointestinal side effects associated with metformin, up to the maximum recommended daily dose.

JANUMET XR should be administered with food to reduce the gastrointestinal side effects associated with the metformin component. JANUMET XR should be given once daily with a meal preferably in the evening. JANUMET XR should be swallowed whole. The tablets must not be split, crushed, or chewed before swallowing.

The 100 mg sitagliptin/1000 mg metformin hydrochloride extended-release tablet should be taken as a single tablet once daily. Patients using two JANUMET XR tablets (such as two 50 mg sitagliptin/500 mg metformin hydrochloride extended-release tablets or two 50 mg sitagliptin/1000 mg metformin hydrochloride extended-release tablets) should take the two tablets together once daily.

Patients treated with an insulin secretagogue or insulin

Co-administration of JANUMET XR with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin 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 XR in patients previously treated with other oral antihyperglycemic agents and switched to JANUMET XR. 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

- 100 mg/1000 mg tablets are blue, bi-convex oval, film-coated tablets with “81” debossed on one side.
- 50 mg/500 mg tablets are light blue, bi-convex oval, film-coated tablets with “78” debossed on one side.
- 50 mg/1000 mg tablets are light green, bi-convex oval, film-coated tablets with “80” debossed on one side.

4 CONTRAINDICATIONS

JANUMET XR is contraindicated in patients with:

- Renal impairment (e.g., serum creatinine levels greater than or equal to 1.5 mg/dL for men, greater than or equal to 1.4 mg/dL for women 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)]*.
- Hypersensitivity to metformin hydrochloride.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
- History of a serious hypersensitivity reaction to JANUMET XR or sitagliptin, such as anaphylaxis or angioedema. *[See Warnings and Precautions (5.14); Adverse Reactions (6.2).]*

5 WARNINGS AND PRECAUTIONS

5.1 Lactic Acidosis

Metformin hydrochloride

Lactic acidosis is a serious, metabolic complication that can occur due to metformin accumulation during treatment with JANUMET XR and 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 concentrations (>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 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 impairment, 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 JANUMET XR. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. JANUMET XR treatment should not be initiated in any patient unless measurement of creatinine clearance demonstrates that renal function is not reduced. In addition, JANUMET XR 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, JANUMET XR should generally be avoided in patients with clinical or laboratory evidence of hepatic impairment. Patients should be cautioned against excessive alcohol intake when taking JANUMET XR, because alcohol potentiates the effects of metformin on lactate metabolism. In addition, JANUMET XR should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure necessitating restricted intake of food or fluids. Use of topiramate, a carbonic anhydrase inhibitor, in epilepsy and migraine prophylaxis may frequently cause dose-dependent metabolic acidosis (in controlled trials, 32% and 67% for adjunctive treatment in adults and pediatric patients, respectively, and 15 to 25% for monotherapy of epilepsy, with decrease in serum bicarbonate to less than 20 mEq/L; 3% and 11% for adjunctive treatment in adults and pediatric patients, respectively, and 1 to 7% for monotherapy of epilepsy, with decrease in serum bicarbonate to less than 17 mEq/L) and may exacerbate the risk of metformin-induced lactic acidosis. *[See Drug Interactions (7.1); Clinical Pharmacology (12).]* 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.

Patients should be educated to promptly report these symptoms to their physician should they occur. If present, JANUMET XR should be withdrawn until lactic acidosis is ruled out. Serum electrolytes, ketones, blood glucose, blood pH, lactate levels, and blood metformin levels may be useful. Once a patient is stabilized on any dose level of JANUMET XR, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to recur. 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 JANUMET XR 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. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia). Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking JANUMET XR, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. *[See Contraindications (4).]*

5.2 Pancreatitis

There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking sitagliptin with or without metformin. After initiation of JANUMET XR, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, JANUMET XR should promptly be discontinued and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using JANUMET XR.

5.3 Impaired Hepatic Function

Since impaired hepatic function has been associated with some cases of lactic acidosis, JANUMET XR should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

5.4 Assessment of Renal Function

Metformin and sitagliptin are substantially excreted by the kidney.

Metformin hydrochloride

The risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Therefore, JANUMET XR is contraindicated in patients with renal impairment.

Before initiation of JANUMET XR and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated (e.g., elderly),

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