

## 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.

- 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 XR and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. (5.1)

#### 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)
- 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 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 m<sup>2</sup>.
  - Discontinue if eGFR later falls below 30 mL/min/1.73 m<sup>2</sup>.
  - Initiation is not recommended in patients with eGFR between 30 – 45 mL/min/1.73 m<sup>2</sup>.
  - Assess risk/benefit of continuing if eGFR falls below 45 mL/min/1.73 m<sup>2</sup>.
  - Limit dose of sitagliptin to 50 mg once daily if eGFR falls below 45 mL/min/1.73 m<sup>2</sup>.
- JANUMET XR may need to be discontinued at time of, or prior to, iodinated contrast imaging procedures. (2.3)

#### 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

- Severe renal impairment: eGFR below 30 mL/min/1.73 m<sup>2</sup>. (4)
- Metabolic acidosis, including diabetic ketoacidosis. (4)
- History of a serious hypersensitivity reaction (e.g., anaphylaxis or angioedema) to JANUMET XR or to one of its components. (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 in patients treated with sitagliptin. If pancreatitis is suspected, promptly discontinue JANUMET XR. (5.2)
- Heart failure has been observed with two other members of the DPP-4 inhibitor class. Consider risks and benefits of JANUMET XR in 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 in patients treated with sitagliptin, sometimes requiring dialysis. Before initiating JANUMET XR and at least annually thereafter, assess renal function. (5.4)
- Vitamin B<sub>12</sub> deficiency: Metformin may lower Vitamin B<sub>12</sub> 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 minimize the risk of hypoglycemia. (5.7)
- 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. (5.9)
- 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 XR. (5.11)
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with JANUMET XR. (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](http://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

- 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)
- 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 XR and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended [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. There have been reports of incompletely dissolved JANUMET XR tablets being eliminated in the feces. It is not known whether this material seen in feces contains active drug. If a patient reports repeatedly seeing tablets in feces, the health care provider should assess adequacy of glycemic control [see *Patient Counseling Information* (17.1)].

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.

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.

### 2.2 Recommendations for Use in Renal Impairment

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

JANUMET XR is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m<sup>2</sup>. Discontinue JANUMET XR if the patient's eGFR later falls below 30 mL/min/1.73 m<sup>2</sup> [see *Contraindications* (4) and *Warnings and Precautions* (5.1)].

Initiation of JANUMET XR in patients with an eGFR between 30 and 45 mL/min/1.73 m<sup>2</sup> is not recommended.

In patients taking JANUMET XR whose eGFR later falls below 45 mL/min/1.73 m<sup>2</sup>, assess the benefit risk of continuing therapy and limit dose of the sitagliptin component to 50 mg once daily.

### 2.3 Discontinuation for Iodinated Contrast Imaging Procedures

Discontinue JANUMET XR 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 m<sup>2</sup>; 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 XR if renal function is stable [see *Warnings and Precautions* (5.1)].

### 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:

- Severe renal impairment (eGFR below 30 mL/min/1.73 m<sup>2</sup>) [*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 (5.9); Adverse Reactions (6.2).*]

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Lactic Acidosis

##### *Metformin hydrochloride*

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 XR. In JANUMET XR-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin hydrochloride 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 XR 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 XR, obtain an estimated glomerular filtration rate (eGFR).
- JANUMET XR is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m<sup>2</sup>. Discontinue JANUMET XR if the patient's eGFR later falls below 30 mL/min/1.73 m<sup>2</sup> [*see Contraindications (4)*].

- Initiation of JANUMET XR is not recommended in patients with eGFR between 30 and 45 mL/min/1.73 m<sup>2</sup>.
- In patients taking JANUMET XR whose eGFR later falls below 45 mL/min/1.73 m<sup>2</sup>, assess the benefit and risk of continuing therapy.
- Obtain an eGFR at least annually in all patients taking JANUMET XR. 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 XR 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 XR 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 m<sup>2</sup>; 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 XR 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 XR 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 XR.

#### *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 XR.

#### *Hepatic Impairment*

Patients with hepatic impairment have developed with cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of JANUMET XR in patients with clinical or laboratory evidence of hepatic disease.

### **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 Heart Failure

An association between dipeptidyl peptidase-4 (DPP-4) inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease.

Consider the risks and benefits of JANUMET XR prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment, and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of JANUMET XR.

### 5.4 Assessment of Renal Function

Metformin and sitagliptin are substantially excreted by the kidney.

#### *Metformin hydrochloride*

JANUMET XR is contraindicated in patients with severe renal impairment [see *Contraindications (4) and Warnings and Precautions (5.1)*].

#### *Sitagliptin*

There have been postmarketing reports of worsening renal function in patients taking sitagliptin with or without metformin, including acute renal failure, sometimes requiring dialysis. Before initiation of therapy with JANUMET XR and at least annually thereafter, renal function should be assessed. In patients in whom development of renal dysfunction is anticipated, particularly in elderly patients, renal function should be assessed more frequently and JANUMET XR discontinued if evidence of renal impairment is present.

### 5.5 Vitamin B<sub>12</sub> Levels

In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B<sub>12</sub> levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B<sub>12</sub> absorption from the B<sub>12</sub>-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B<sub>12</sub> supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on JANUMET XR and any apparent abnormalities should be appropriately investigated and managed. [See *Adverse Reactions (6.1)*.]

Certain individuals (those with inadequate Vitamin B<sub>12</sub> or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B<sub>12</sub> levels. In these patients, routine serum Vitamin B<sub>12</sub> measurements at two- to three-year intervals may be useful.

### 5.6 Change in Clinical Status of Patients with Previously Controlled Type 2 Diabetes

A patient with type 2 diabetes previously well controlled on JANUMET XR who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, JANUMET XR must be stopped immediately and other appropriate corrective measures initiated.

### 5.7 Use with Medications Known to Cause Hypoglycemia

#### *Sitagliptin*

When sitagliptin was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin [see *Adverse Reactions (6)*]. Therefore, patients also receiving an insulin secretagogue (e.g., sulfonylurea) or insulin may require a lower dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia [see *Drug Interactions (7.4)*].

#### *Metformin hydrochloride*

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking  $\beta$ -adrenergic blocking drugs.

### 5.8 Loss of Control of Blood Glucose

When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary

to withhold JANUMET XR and temporarily administer insulin. JANUMET XR may be reinstituted after the acute episode is resolved.

### **5.9 Hypersensitivity Reactions**

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, one of the components of JANUMET XR. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue JANUMET XR, assess for other potential causes for the event, and institute alternative treatment for diabetes. [See *Adverse Reactions* (6.2).]

Use caution in a patient with a history of angioedema to another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with JANUMET XR.

### **5.10 Severe and Disabling Arthralgia**

There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

### **5.11 Bullous Pemphigoid**

Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving JANUMET XR. If bullous pemphigoid is suspected, JANUMET XR should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

### **5.12 Macrovascular Outcomes**

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with JANUMET XR.

## **6 ADVERSE REACTIONS**

### **6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

*Sitagliptin and Metformin Immediate-Release Coadministration in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise*

Table 1 summarizes the most common ( $\geq 5\%$  of patients) adverse reactions reported (regardless of investigator assessment of causality) in a 24-week placebo-controlled factorial study in which sitagliptin and metformin immediate-release were coadministered to patients with type 2 diabetes inadequately controlled on diet and exercise.

**Table 1: Sitagliptin and Metformin Immediate-Release Coadministered to Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise: Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in ≥5% of Patients Receiving Combination Therapy (and Greater than in Patients Receiving Placebo) \***

	Number of Patients (%)			
	Placebo	Sitagliptin 100 mg once daily	Metformin Immediate-Release 500 mg or 1000 mg twice daily †	Sitagliptin 50 mg twice daily + Metformin Immediate-Release 500 mg or 1000 mg twice daily †
	<b>N = 176</b>	<b>N = 179</b>	<b>N = 364†</b>	<b>N = 372†</b>
Diarrhea	7 (4.0)	5 (2.8)	28 (7.7)	28 (7.5)
Upper Respiratory Tract Infection	9 (5.1)	8 (4.5)	19 (5.2)	23 (6.2)
Headache	5 (2.8)	2 (1.1)	14 (3.8)	22 (5.9)

\* Intent-to-treat population.

† Data pooled for the patients given the lower and higher doses of metformin.

*Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on Metformin Immediate-Release Alone*

In a 24-week placebo-controlled trial of sitagliptin 100 mg administered once daily added to a twice daily metformin immediate-release regimen, there were no adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients and more commonly than in patients given placebo. Discontinuation of therapy due to clinical adverse reactions was similar to the placebo treatment group (sitagliptin and metformin immediate-release, 1.9%; placebo and metformin immediate-release, 2.5%).

*Gastrointestinal Adverse Reactions*

The incidences of pre-selected gastrointestinal adverse experiences in patients treated with sitagliptin and metformin immediate-release were similar to those reported for patients treated with metformin immediate-release alone. See Table 2.

**Table 2: Pre-selected Gastrointestinal Adverse Reactions (Regardless of Investigator Assessment of Causality) Reported in Patients with Type 2 Diabetes Receiving Sitagliptin and Metformin Immediate-Release**

	Number of Patients (%)					
	Study of Sitagliptin and Metformin Immediate-Release in Patients Inadequately Controlled on Diet and Exercise				Study of Sitagliptin Add-on in Patients Inadequately Controlled on Metformin Immediate-Release Alone	
	Placebo	Sitagliptin 100 mg once daily	Metformin Immediate-Release 500 mg or 1000 mg twice daily *	Sitagliptin 50 mg bid + Metformin Immediate-Release 500 mg or 1000 mg twice daily *	Placebo and Metformin Immediate-Release ≥1500 mg daily	Sitagliptin 100 mg once daily and Metformin Immediate-Release ≥1500 mg daily
	<b>N = 176</b>	<b>N = 179</b>	<b>N = 364</b>	<b>N = 372</b>	<b>N = 237</b>	<b>N = 464</b>
Diarrhea	7 (4.0)	5 (2.8)	28 (7.7)	28 (7.5)	6 (2.5)	11 (2.4)
Nausea	2 (1.1)	2 (1.1)	20 (5.5)	18 (4.8)	2 (0.8)	6 (1.3)
Vomiting	1 (0.6)	0 (0.0)	2 (0.5)	8 (2.2)	2 (0.8)	5 (1.1)
Abdominal Pain†	4 (2.3)	6 (3.4)	14 (3.8)	11 (3.0)	9 (3.8)	10 (2.2)

\* Data pooled for the patients given the lower and higher doses of metformin.

† Abdominal discomfort was included in the analysis of abdominal pain in the study of initial therapy.

*Sitagliptin in Combination with Metformin Immediate-Release and Glimepiride*

In a 24-week placebo-controlled study of sitagliptin 100 mg as add-on therapy in patients with type 2 diabetes inadequately controlled on metformin immediate-release and glimepiride (sitagliptin, N=116;



placebo, N=113), the adverse reactions reported regardless of investigator assessment of causality in  $\geq 5\%$  of patients treated with sitagliptin and more commonly than in patients treated with placebo were: hypoglycemia (Table 3) and headache (6.9%, 2.7%).

#### *Sitagliptin in Combination with Metformin Immediate-Release and Rosiglitazone*

In a placebo-controlled study of sitagliptin 100 mg as add-on therapy in patients with type 2 diabetes inadequately controlled on metformin immediate-release and rosiglitazone (sitagliptin, N=181; placebo, N=97), the adverse reactions reported regardless of investigator assessment of causality through Week 18 in  $\geq 5\%$  of patients treated with sitagliptin and more commonly than in patients treated with placebo were: upper respiratory tract infection (sitagliptin, 5.5%; placebo, 5.2%) and nasopharyngitis (6.1%, 4.1%). Through Week 54, the adverse reactions reported regardless of investigator assessment of causality in  $\geq 5\%$  of patients treated with sitagliptin and more commonly than in patients treated with placebo were: upper respiratory tract infection (sitagliptin, 15.5%; placebo, 6.2%), nasopharyngitis (11.0%, 9.3%), peripheral edema (8.3%, 5.2%), and headache (5.5%, 4.1%).

#### *Sitagliptin in Combination with Metformin Immediate-Release and Insulin*

In a 24-week placebo-controlled study of sitagliptin 100 mg as add-on therapy in patients with type 2 diabetes inadequately controlled on metformin immediate-release and insulin (sitagliptin, N=229; placebo, N=233), the only adverse reaction reported regardless of investigator assessment of causality in  $\geq 5\%$  of patients treated with sitagliptin and more commonly than in patients treated with placebo was hypoglycemia (Table 3).

#### *Hypoglycemia*

In all (N=5) studies, adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia; a concurrent glucose measurement was not required although most (77%) reports of hypoglycemia were accompanied by a blood glucose measurement  $\leq 70$  mg/dL. When the combination of sitagliptin and metformin immediate-release was coadministered with a sulfonylurea or with insulin, the percentage of patients reporting at least one adverse reaction of hypoglycemia was higher than that observed with placebo and metformin immediate-release coadministered with a sulfonylurea or with insulin (Table 3).

**Table 3: Incidence and Rate of Hypoglycemia\* (Regardless of Investigator Assessment of Causality) in Placebo-Controlled Clinical Studies of Sitagliptin in Combination with Metformin Immediate-Release Coadministered with Glimepiride or Insulin**

<b>Add-On to Glimepiride + Metformin Immediate-Release (24 weeks)</b>	<b>Sitagliptin 100 mg + Metformin Immediate-Release + Glimepiride</b>	<b>Placebo + Metformin Immediate-Release + Glimepiride</b>
	N = 116	N = 113
Overall (%)	19 (16.4)	1 (0.9)
Rate (episodes/patient-year) <sup>†</sup>	0.82	0.02
Severe (%) <sup>‡</sup>	0 (0.0)	0 (0.0)
<b>Add-On to Insulin + Metformin Immediate-Release (24 weeks)</b>	<b>Sitagliptin 100 mg + Metformin Immediate-Release + Insulin</b>	<b>Placebo + Metformin Immediate-Release + Insulin</b>
	N = 229	N = 233
Overall (%)	35 (15.3)	19 (8.2)
Rate (episodes/patient-year) <sup>†</sup>	0.98	0.61
Severe (%) <sup>‡</sup>	1 (0.4)	1 (0.4)

\* Adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia; a concurrent glucose measurement was not required: Intent-to-treat population.

<sup>†</sup> Based on total number of events (i.e., a single patient may have had multiple events).

<sup>‡</sup> Severe events of hypoglycemia were defined as those events requiring medical assistance or exhibiting depressed level/loss of consciousness or seizure.

The overall incidence of reported adverse reactions of hypoglycemia in patients with type 2 diabetes inadequately controlled on diet and exercise was 0.6% in patients given placebo, 0.6% in patients given sitagliptin alone, 0.8% in patients given metformin immediate-release alone, and 1.6% in patients given sitagliptin in combination with metformin immediate-release. In patients with type 2 diabetes inadequately

controlled on metformin immediate-release alone, the overall incidence of adverse reactions of hypoglycemia was 1.3% in patients given add-on sitagliptin and 2.1% in patients given add-on placebo.

In the study of sitagliptin and add-on combination therapy with metformin immediate-release and rosiglitazone, the overall incidence of hypoglycemia was 2.2% in patients given add-on sitagliptin and 0.0% in patients given add-on placebo through Week 18. Through Week 54, the overall incidence of hypoglycemia was 3.9% in patients given add-on sitagliptin and 1.0% in patients given add-on placebo.

#### *Vital Signs and Electrocardiograms*

With the combination of sitagliptin and metformin immediate-release, no clinically meaningful changes in vital signs or in electrocardiogram parameters (including the QTc interval) were observed.

#### *Pancreatitis*

In a pooled analysis of 19 double-blind clinical trials that included data from 10,246 patients randomized to receive sitagliptin 100 mg/day (N=5429) or corresponding (active or placebo) control (N=4817), the incidence of acute pancreatitis was 0.1 per 100 patient-years in each group (4 patients with an event in 4708 patient-years for sitagliptin and 4 patients with an event in 3942 patient-years for control).

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

#### *Sitagliptin*

The most common adverse experience in sitagliptin monotherapy reported regardless of investigator assessment of causality in  $\geq 5\%$  of patients and more commonly than in patients given placebo was nasopharyngitis.

#### *Metformin Extended-Release*

In a 24-week clinical trial in which extended-release metformin or placebo was added to glyburide therapy, the most common ( $>5\%$  and greater than placebo) adverse reactions in the combined treatment group were hypoglycemia (13.7% vs. 4.9%), diarrhea (12.5% vs. 5.6%), and nausea (6.7% vs. 4.2%).

#### *Laboratory Tests*

##### *Sitagliptin*

The incidence of laboratory adverse reactions was similar in patients treated with sitagliptin and metformin immediate-release (7.6%) compared to patients treated with placebo and metformin (8.7%). In most but not all studies, a small increase in white blood cell count (approximately 200 cells/microL difference in WBC vs. placebo; mean baseline WBC approximately 6600 cells/microL) was observed due to a small increase in neutrophils. This change in laboratory parameters is not considered to be clinically relevant.

##### *Metformin hydrochloride*

In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B<sub>12</sub> levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B<sub>12</sub> absorption from the B<sub>12</sub>-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B<sub>12</sub> supplementation. [See *Warnings and Precautions* (5.5).]

## **6.2 Postmarketing Experience**

Additional adverse reactions have been identified during postapproval use of sitagliptin with metformin, sitagliptin, or metformin. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome [see *Warnings and Precautions* (5.9)]; upper respiratory tract infection; hepatic enzyme elevations; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis [see *Indications and Usage* (1); *Warnings and Precautions* (5.2)]; worsening renal function, including acute renal failure (sometimes requiring dialysis) [see *Warnings and Precautions* (5.4)]; severe and disabling arthralgia [see *Warnings and Precautions* (5.10)]; bullous pemphigoid [see *Warnings and Precautions* (5.11)]; constipation; vomiting; headache; myalgia; pain in extremity; back pain; pruritus; mouth ulceration; stomatitis; cholestatic, hepatocellular, and mixed hepatocellular liver injury; rhabdomyolysis.

## 7 DRUG INTERACTIONS

### 7.1 Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with JANUMET XR may increase the risk of lactic acidosis. Consider more frequent monitoring of these patients.

### 7.2 Drugs that Reduce Metformin Clearance

Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis [see *Clinical Pharmacology* (12.3)]. Consider the benefits and risks of concomitant use.

### 7.3 Alcohol

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving JANUMET XR.

### 7.4 Insulin Secretagogues or Insulin

Coadministration 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* (5.7).]

### 7.5 Use of Metformin with Other Drugs

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving JANUMET XR the patient should be closely observed to maintain adequate glycemic control.

### 7.6 Digoxin

There was a slight increase in the area under the curve (AUC, 11%) and mean peak drug concentration ( $C_{max}$ , 18%) of digoxin with the coadministration of 100 mg sitagliptin for 10 days. Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or JANUMET XR is recommended.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to JANUMET XR during pregnancy. Health care providers are encouraged to report any prenatal exposure to JANUMET XR by calling the Pregnancy Registry at 1-800-986-8999.

#### Risk Summary

The limited available data with JANUMET XR in pregnant women are not sufficient to inform a drug-associated risk for major birth defects and miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk [see *Data*]. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy [see *Clinical Considerations*]. No adverse developmental effects were observed when sitagliptin was administered to pregnant rats and rabbits during organogenesis at oral doses up to 30-times and 20-times, respectively, the 100 mg clinical dose, based on AUC. No adverse developmental effects were observed when metformin was administered to pregnant Sprague Dawley rats and rabbits during organogenesis at doses up to 2- and 6-times, respectively, a 2000 mg clinical dose, based on body surface area [see *Data*].

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a Hemoglobin A1c >7% and has been reported to be as high as 20-25% in women with a Hemoglobin A1c >10%. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

#### Clinical Considerations

#### *Disease-Associated Maternal and/or Embryo/Fetal Risk*

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, still birth, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

## Data

### *Human Data*

Published data from post-marketing studies do not report a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin is used during pregnancy. However, these studies cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and inconsistent comparator groups.

### *Animal Data*

#### *Sitagliptin and Metformin*

No animal reproduction studies were conducted with the coadministration of sitagliptin and metformin.

#### *Sitagliptin*

In embryo-fetal development studies, sitagliptin administered to pregnant rats and rabbits during organogenesis (gestation day 6 to 20) did not adversely affect developmental outcomes at oral doses up to 250 mg/kg (30-times the 100 mg clinical dose) and 125 mg/kg (20-times the 100 mg clinical dose), respectively, based on AUC. Higher doses in rats associated with maternal toxicity increased the incidence of rib malformations in offspring at 1000 mg/kg, or approximately 100-times the clinical dose, based on AUC. Placental transfer of sitagliptin was observed in pregnant rats and rabbits.

Sitagliptin administered to female rats from gestation day 6 to lactation day 21 caused no functional or behavioral toxicity in offspring of rats at doses up to 1000 mg/kg.

#### *Metformin hydrochloride*

Metformin hydrochloride did not cause adverse developmental effects when administered to pregnant Sprague Dawley rats and rabbits up to 600 mg/kg/day during the period of organogenesis. This represents an exposure of about 2- and 6-times a 2000 mg clinical dose based on body surface area (mg/m<sup>2</sup>) for rats and rabbits, respectively.

## **8.2 Lactation**

### Risk Summary

There is no information regarding the presence of JANUMET XR in human milk, the effects on the breastfed infant, or the effects on milk production. Limited published studies report that metformin is present in human milk [see *Data*]. There are no reports of adverse effects on breastfed infants exposed to metformin. There is no information on the effects of metformin on milk production. Sitagliptin is present in rat milk and therefore possibly present in human milk [see *Data*]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for JANUMET XR and any potential adverse effects on the breastfed infant from JANUMET XR or from the underlying maternal condition.

## Data

### *Sitagliptin*

Sitagliptin is secreted in the milk of lactating rats at a milk to plasma ratio of 4:1.

### *Metformin hydrochloride*

Published clinical lactation studies report that metformin is present in human milk, which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants.

## **8.3 Females and Males of Reproductive Potential**

Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women.

## **8.4 Pediatric Use**

Safety and effectiveness of JANUMET XR in pediatric patients under 18 years have not been established.

## 8.5 Geriatric Use

### JANUMET XR

Because sitagliptin and metformin are substantially excreted by the kidney, and because aging can be associated with reduced renal function, renal function should be assessed more frequently in elderly patients. [See *Warnings and Precautions* (5.1, 5.4); *Clinical Pharmacology* (12.3).]

#### *Sitagliptin*

Of the total number of subjects (N=3884) in premarketing Phase II and III clinical studies of sitagliptin, 725 patients were 65 years and over, while 61 patients were 75 years and over. No overall differences in safety or effectiveness were observed between subjects 65 years and over and younger subjects. While this and other reported clinical experience have not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

#### *Metformin hydrochloride*

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal function more frequently in elderly patients. [See *Contraindications* (4); *Warnings and Precautions* (5.4); *Clinical Pharmacology* (12.3).]

## 8.6 Renal Impairment

### JANUMET XR

The dose of the sitagliptin component should be limited to 50 mg once daily if eGFR falls below 45 mL/min/1.73 m<sup>2</sup>. JANUMET XR is contraindicated in severe renal impairment, patients with an eGFR below 30 mL/min/1.73 m<sup>2</sup>. [See *Dosage and Administration* (2.2), *Contraindications* (4), *Warnings and Precautions* (5.1) and *Clinical Pharmacology* (12.3).]

#### *Sitagliptin*

Sitagliptin is excreted by the kidney, and sitagliptin exposure is increased in patients with renal impairment. Lower dosages are recommended in patients with eGFR less than 45 mL/min/1.73 m<sup>2</sup> (moderate and severe renal impairment, as well as in ESRD patients requiring dialysis).

#### *Metformin hydrochloride*

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment.

## 8.7 Hepatic Impairment

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. JANUMET XR is not recommended in patients with hepatic impairment. [See *Warnings and Precautions* (5.1).]

## 10 OVERDOSAGE

### *Sitagliptin*

During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were administered. Maximal mean increases in QTc of 8.0 msec were observed in one study at a dose of 800 mg sitagliptin, a mean effect that is not considered clinically important [see *Clinical Pharmacology* (12.2)]. There is no experience with doses above 800 mg in clinical studies. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 400 mg per day for periods of up to 28 days.

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy as indicated by the patient's clinical status.

Sitagliptin is modestly dialyzable. In clinical studies, approximately 13.5% of the dose was removed over a 3- to 4-hour hemodialysis session. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialyzable by peritoneal dialysis.

### Metformin hydrochloride

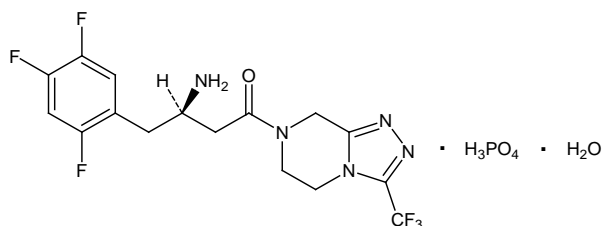
Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases [see *Warnings and Precautions* (5.1)]. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

## 11 DESCRIPTION

JANUMET XR tablets contain two oral antidiabetic medications used in the management of type 2 diabetes: sitagliptin and metformin hydrochloride extended-release.

### Sitagliptin

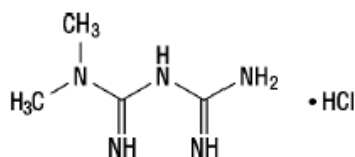
Sitagliptin is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme. Sitagliptin phosphate monohydrate drug substance is used to manufacture JANUMET XR. Sitagliptin phosphate monohydrate is described chemically as 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3- $\alpha$ ]pyrazine phosphate (1:1) monohydrate with an empirical formula of  $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$  and a molecular weight of 523.32. The structural formula is:



Sitagliptin phosphate monohydrate is a white to off-white, crystalline, non-hygroscopic powder. It is soluble in water and N,N-dimethyl formamide; slightly soluble in methanol; very slightly soluble in ethanol, acetone, and acetonitrile; and insoluble in isopropanol and isopropyl acetate.

### Metformin hydrochloride

Metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is a white to off-white crystalline compound with a molecular formula of  $C_4H_{11}N_5 \cdot HCl$  and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The  $pK_a$  of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural formula is as shown:



### JANUMET XR

JANUMET XR consists of an extended-release metformin core tablet coated with an immediate-release layer of sitagliptin. The sitagliptin layer is coated with a soluble polymeric film. JANUMET XR is available for oral administration as tablets containing 64.25 mg sitagliptin phosphate monohydrate (equivalent to 50 mg sitagliptin as free base) and either 500 mg metformin hydrochloride extended-release (50 mg/500 mg) or 1000 mg metformin hydrochloride extended-release (50 mg/1000 mg). Additionally, JANUMET XR is available for oral administration as tablets containing 128.5 mg sitagliptin phosphate monohydrate (equivalent to 100 mg sitagliptin as free base) and 1000 mg metformin hydrochloride extended-release (100 mg/1000 mg).

All doses of JANUMET XR contain the following inactive ingredients: povidone, hypromellose, colloidal silicon dioxide, sodium stearyl fumarate, propyl gallate, polyethylene glycol, and kaolin. The JANUMET XR 50 mg/500 mg tablet contains the additional inactive ingredient microcrystalline cellulose. In addition, the film coating for all doses contains the following inactive ingredients: hypromellose, hydroxypropyl cellulose, titanium dioxide, FD&C #2/Indigo Carmine Aluminum Lake and carnauba wax. The JANUMET XR 50 mg/1000 mg tablet film coating also contains the inactive ingredient yellow iron oxide.

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

#### *JANUMET XR*

JANUMET XR tablets combine two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in adults with type 2 diabetes mellitus: sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin hydrochloride extended-release, a member of the biguanide class.

#### *Sitagliptin*

Sitagliptin is a DPP-4 inhibitor, which exerts its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased by sitagliptin, thereby increasing and prolonging the action of these hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. These hormones are rapidly inactivated by the enzyme DPP-4. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling pathways involving cyclic AMP. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner. Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity *in vitro* at concentrations approximating those from therapeutic doses.

#### *Metformin hydrochloride*

Metformin is a biguanide that improves glycemic control in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin does not produce hypoglycemia in either patients with type 2 diabetes mellitus or healthy subjects except in certain circumstances [see *Warnings and Precautions* (5.7)] and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

### **12.2 Pharmacodynamics**

#### *Sitagliptin*

In patients with type 2 diabetes mellitus, administration of sitagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP-4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased responsiveness of insulin release to glucose, resulting in higher C-peptide and insulin concentrations. The rise in insulin with the decrease in glucagon was associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

In studies with healthy subjects, sitagliptin did not lower blood glucose or cause hypoglycemia.

#### *Sitagliptin and Metformin hydrochloride Coadministration*

In a two-day study in healthy subjects, sitagliptin alone increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Coadministration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations. It is unclear what these findings mean for changes in glycemic control in patients with type 2 diabetes mellitus.

### *Cardiac Electrophysiology*

In a randomized, placebo-controlled crossover study, 79 healthy subjects were administered a single oral dose of sitagliptin 100 mg, sitagliptin 800 mg (8 times the recommended dose), and placebo. At the recommended dose of 100 mg, there was no effect on the QTc interval obtained at the peak plasma concentration, or at any other time during the study. Following the 800-mg dose, the maximum increase in the placebo-corrected mean change in QTc from baseline at 3 hours postdose was 8.0 msec. This increase is not considered to be clinically significant. At the 800-mg dose, peak sitagliptin plasma concentrations were approximately 11 times higher than the peak concentrations following a 100-mg dose.

In patients with type 2 diabetes mellitus administered sitagliptin 100 mg (N=81) or sitagliptin 200 mg (N=63) daily, there were no meaningful changes in QTc interval based on ECG data obtained at the time of expected peak plasma concentration.

### **12.3 Pharmacokinetics**

#### *JANUMET XR*

After administration of two JANUMET XR 50 mg/1000 mg tablets once daily with the evening meal for 7 days in healthy adult subjects, steady-state for sitagliptin and metformin is reached by Day 4 and 5, respectively.

#### *Sitagliptin*

The pharmacokinetics of sitagliptin have been extensively characterized in healthy subjects and patients with type 2 diabetes mellitus. Following a single oral 100-mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8.52  $\mu\text{M}\cdot\text{hr}$ ,  $C_{\text{max}}$  was 950 nM, and apparent terminal half-life ( $t_{1/2}$ ) was 12.4 hours. Plasma AUC of sitagliptin increased in a dose-proportional manner and increased approximately 14% following 100 mg doses at steady-state compared to the first dose. The intra-subject and inter-subject coefficients of variation for sitagliptin AUC were small (5.8% and 15.1%). The pharmacokinetics of sitagliptin was generally similar in healthy subjects and in patients with type 2 diabetes mellitus.

#### *Absorption*

#### *JANUMET XR*

After administration of JANUMET XR tablets once daily, the median  $T_{\text{max}}$  value for sitagliptin and metformin at steady state is approximately 3 and 8 hours postdose, respectively. The median  $T_{\text{max}}$  value for sitagliptin and metformin after administration of a single tablet of JANUMET is 3 and 3.5 hours postdose, respectively.

#### *Effect of Food*

After administration of JANUMET XR tablets with a high-fat breakfast, the AUC for sitagliptin was not altered. The mean  $C_{\text{max}}$  was decreased by 17%, although the median  $T_{\text{max}}$  was unchanged relative to the fasted state. After administration of JANUMET XR with a high-fat breakfast, the AUC for metformin increased 62%, the  $C_{\text{max}}$  for metformin decreased by 9%, and the median  $T_{\text{max}}$  for metformin occurred 2 hours later relative to the fasted state.

#### *Sitagliptin*

After oral administration of a 100 mg dose to healthy subjects, sitagliptin was rapidly absorbed with peak plasma concentrations (median  $T_{\text{max}}$ ) occurring 1 to 4 hours postdose. The absolute bioavailability of sitagliptin is approximately 87%.

#### *Effect of Food*

Coadministration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics of sitagliptin.

#### *Metformin hydrochloride*

The absolute bioavailability of a metformin hydrochloride 500-mg tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of metformin hydrochloride tablets 500 mg to 1,500 mg, and 850 mg to 2,550 mg (approximately 1.3 times the maximum recommended daily dosage), indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination.

#### *Effect of Food*



Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration ( $C_{max}$ ), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration ( $T_{max}$ ) following administration of a single 850-mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

#### *Distribution*

##### *Sitagliptin*

The mean volume of distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subjects is approximately 198 liters. The fraction of sitagliptin reversibly bound to plasma proteins is low (38%).

##### *Metformin hydrochloride*

Distribution studies with extended-release metformin have not been conducted; however, the apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin hydrochloride tablets 850 mg averaged  $654 \pm 358$  L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin hydrochloride tablets, steady-state plasma concentrations of metformin are reached within 24-48 hours and are generally  $< 1$  mcg/mL. During controlled clinical trials of metformin, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

#### *Elimination*

##### *Sitagliptin*

Approximately 79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination. The apparent terminal  $t_{1/2}$  following a 100 mg oral dose of sitagliptin was approximately 12.4 hours and renal clearance was approximately 350 mL/min.

##### *Metformin hydrochloride*

Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

#### *Metabolism*

##### *Sitagliptin*

Following a [ $^{14}$ C]sitagliptin oral dose, approximately 16% of the radioactivity was excreted as metabolites of sitagliptin. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. *In vitro* studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.

##### *Metformin hydrochloride*

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion. Metabolism studies with extended-release metformin tablets have not been conducted.

#### *Excretion*

##### *Sitagliptin*

Following administration of an oral [ $^{14}$ C]sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in feces (13%) or urine (87%) within one week of dosing.

Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), which may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of p-glycoprotein (P-gp), which may also be involved in mediating the renal elimination of sitagliptin. However, cyclosporine, a P-gp inhibitor, did not reduce the renal clearance of sitagliptin.

### *Metformin hydrochloride*

Elimination of metformin occurs primarily via renal excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination.

### *Specific Populations*

#### *Patients with Renal Impairment*

##### JANUMET XR

Studies characterizing the pharmacokinetics of sitagliptin and metformin after administration of JANUMET XR in renally impaired patients have not been performed [see *Dosage and Administration* (2.2)].

##### *Sitagliptin*

An approximately 2-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal impairment with eGFR of 30 to less than 45 mL/min/1.73 m<sup>2</sup>, and an approximately 4-fold increase was observed in patients with severe renal impairment including patients with end-stage renal disease (ESRD) on hemodialysis, as compared to normal healthy control subjects. [See *Dosage and Administration* (2.2).]

### *Metformin hydrochloride*

In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased [see *Contraindications* (4), *Warnings and Precautions* (5.1)].

#### *Patients with Hepatic Impairment*

##### JANUMET XR

Studies characterizing the pharmacokinetics of sitagliptin and metformin after administration of JANUMET XR in patients with hepatic impairment have not been performed.

##### *Sitagliptin*

In patients with moderate hepatic impairment (Child-Pugh score 7 to 9), mean AUC and C<sub>max</sub> of sitagliptin increased approximately 21% and 13%, respectively, compared to healthy matched controls following administration of a single 100-mg dose of sitagliptin. These differences are not considered to be clinically meaningful. There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score >9) [see *Use in Specific Populations* (8.7)].

### *Metformin hydrochloride*

No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

#### *Effects of Age, Body Mass Index (BMI), Gender, and Race*

##### *Sitagliptin*

Based on a population pharmacokinetic analysis or a composite analysis of available pharmacokinetic data, BMI, gender, and race do not have a clinically meaningful effect on the pharmacokinetics of sitagliptin. When the effects of age on renal function are taken into account, age alone did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis. Elderly subjects (65 to 80 years) had approximately 19% higher plasma concentrations of sitagliptin compared to younger subjects.

### *Metformin hydrochloride*

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C<sub>max</sub> is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes mellitus when analyzed according to gender. Similarly, in controlled clinical studies in patients with type 2 diabetes mellitus, the antihyperglycemic effect of metformin was comparable in males and females.

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type 2 diabetes mellitus, the antihyperglycemic effect was comparable in Whites (n=249), Blacks (n=51), and Hispanics (n=24).

#### *Pediatric Patients*

##### *Sitagliptin*

Studies characterizing the pharmacokinetics of sitagliptin in pediatric patients have not been performed.

#### *Drug Interaction Studies*

##### *JANUMET XR*

Coadministration of multiple doses of sitagliptin (50 mg) and metformin (1000 mg) given twice daily did not meaningfully alter the pharmacokinetics of either sitagliptin or metformin in patients with type 2 diabetes.

Pharmacokinetic drug interaction studies with JANUMET XR have not been performed; however, such studies have been conducted with the individual components of JANUMET XR (sitagliptin and metformin hydrochloride extended-release).

##### *Sitagliptin*

#### *In Vitro Assessment of Drug Interactions*

Sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4. Sitagliptin is a P-gp substrate, but does not inhibit P-gp mediated transport of digoxin. Based on these results, sitagliptin is considered unlikely to cause interactions with other drugs that utilize these pathways.

Sitagliptin is not extensively bound to plasma proteins. Therefore, the propensity of sitagliptin to be involved in clinically meaningful drug-drug interactions mediated by plasma protein binding displacement is very low.

#### *In Vivo Assessment of Drug Interactions*

##### *Effects of Sitagliptin on Other Drugs*

In clinical studies, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, digoxin, warfarin, or an oral contraception (ethinyl estradiol and norethindrone) (Table 4), providing *in vivo* evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C8, CYP2C9, P-gp, and organic cationic transporter (OCT).

**Table 4: Effect of Sitagliptin on Systemic Exposure of Coadministered Drugs**

Coadministered Drug	Dose of Coadministered Drug*	Dose of Sitagliptin*	Geometric Mean Ratio (ratio with/without sitagliptin) No Effect = 1.00		
				AUC†	C <sub>max</sub>
No dosing adjustments required for the following:					
Digoxin	0.25 mg‡ once daily for 10 days	100 mg‡ once daily for 10 days	Digoxin	1.11§	1.18
Glyburide	1.25 mg	200 mg‡ once daily for 6 days	Glyburide	1.09	1.01
Simvastatin	20 mg	200 mg‡ once daily for 5 days	Simvastatin	0.85¶	0.80
			Simvastatin Acid	1.12¶	1.06
Rosiglitazone	4 mg	200 mg‡ once daily for 5 days	Rosiglitazone	0.98	0.99
Warfarin	30 mg single dose on day 5	200 mg‡ once daily for 11 days	S(-) Warfarin	0.95	0.89
			R(+) Warfarin	0.99	0.89
Ethinyl estradiol and norethindrone	21 days once daily of 35 µg ethinyl estradiol with norethindrone 0.5 mg x 7 days, 0.75 mg x 7 days, 1.0 mg x 7 days	200 mg‡ once daily for 21 days	Ethinyl estradiol	0.99	0.97
			Norethindrone	1.03	0.98

Metformin	1000 mg <sup>†</sup> twice daily for 14 days	50 mg <sup>‡</sup> twice daily for 7 days	Metformin	1.02 <sup>#</sup>	0.97
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\* All doses administered as single dose unless otherwise specified.

† AUC is reported as AUC<sub>0-∞</sub> unless otherwise specified.

‡ Multiple dose.

§ AUC<sub>0-24hr</sub>.

¶ AUC<sub>0-last</sub>.

# AUC<sub>0-12hr</sub>.

### Effects of Other Drugs on Sitagliptin

Clinical data described below suggest that sitagliptin is not susceptible to clinically meaningful interactions by coadministered medications (Table 5).

**Table 5: Effect of Coadministered Drugs on Systemic Exposure of Sitagliptin**

Coadministered Drug	Dose of Coadministered Drug*	Dose of Sitagliptin*	Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00		
				AUC <sup>†</sup>	C <sub>max</sub>
No dosing adjustments required for the following:					
Cyclosporine	600 mg once daily	100 mg once daily	Sitagliptin	1.29	1.68
Metformin	1000 mg <sup>‡</sup> twice daily for 14 days	50 mg <sup>‡</sup> twice daily for 7 days	Sitagliptin	1.02 <sup>§</sup>	1.05

\* All doses administered as single dose unless otherwise specified.

† AUC is reported as AUC<sub>0-∞</sub> unless otherwise specified.

‡ Multiple dose.

§ AUC<sub>0-12hr</sub>.

### Metformin hydrochloride

**Table 6: Effect of Metformin on Systemic Exposure of Coadministered Drugs**

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin*	Geometric Mean Ratio (ratio with/without metformin) No Effect = 1.00		
				AUC <sup>†</sup>	C <sub>max</sub>
No dosing adjustments required for the following:					
Cimetidine	400 mg	850 mg	Cimetidine	0.95 <sup>‡</sup>	1.01
Glyburide	5 mg	500 mg <sup>§</sup>	Glyburide	0.78 <sup>¶</sup>	0.63 <sup>¶</sup>
Furosemide	40 mg	850 mg	Furosemide	0.87 <sup>¶</sup>	0.69 <sup>¶</sup>
Nifedipine	10 mg	850 mg	Nifedipine	1.10 <sup>‡</sup>	1.08
Propranolol	40 mg	850 mg	Propranolol	1.01 <sup>‡</sup>	0.94
Ibuprofen	400 mg	850 mg	Ibuprofen	0.97 <sup>#</sup>	1.01 <sup>#</sup>

\* All doses administered as single dose unless otherwise specified

† AUC is reported as AUC<sub>0-∞</sub> unless otherwise specified

‡ AUC<sub>0-24hr</sub>

§ GLUMETZA (metformin hydrochloride extended-release tablets) 500 mg

¶ Ratio of arithmetic means, p value of difference <0.05

# Ratio of arithmetic means

**Table 7: Effect of Coadministered Drugs on Systemic Exposure of Metformin**

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin*	Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00		
				AUC <sup>†</sup>	C <sub>max</sub>
No dosing adjustments required for the following:					
Glyburide	5 mg	500 mg <sup>‡</sup>	Metformin <sup>‡</sup>	0.98 <sup>§</sup>	0.99 <sup>§</sup>

Furosemide	40 mg	850 mg	Metformin	1.09 <sup>§</sup>	1.22 <sup>§</sup>
Nifedipine	10 mg	850 mg	Metformin	1.16	1.21
Propranolol	40 mg	850 mg	Metformin	0.90	0.94
Ibuprofen	400 mg	850 mg	Metformin	1.05 <sup>§</sup>	1.07 <sup>§</sup>
<b>Drugs that are eliminated by renal tubular secretion may increase the accumulation of metformin. [See Warnings and Precautions (5.1) and Drug Interactions (7.2).]</b>					
Cimetidine	400 mg	850 mg	Metformin	1.40	1.61
<b>Carbonic anhydrase inhibitors may cause metabolic acidosis [See Warnings and Precautions (5.1) and Drug Interactions (7.1).]</b>					
Topiramate	100 mg <sup>¶</sup>	500 mg <sup>¶</sup>	Metformin	1.25 <sup>¶</sup>	1.17

\* All doses administered as single dose unless otherwise specified

† AUC is reported as AUC<sub>0-∞</sub> unless otherwise specified

‡ GLUMETZA (metformin hydrochloride extended-release tablets) 500 mg

§ Ratio of arithmetic means

¶ Steady state 100 mg Topiramate every 12 hr + metformin 500 mg every 12 hr. AUC = AUC<sub>0-12hr</sub>

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

##### JANUMET XR

No animal studies have been conducted with the combined products in JANUMET XR to evaluate carcinogenesis, mutagenesis or impairment of fertility. The following data are based on the findings in studies with sitagliptin and metformin individually.

##### Sitagliptin

A two-year carcinogenicity study was conducted in male and female rats given oral doses of sitagliptin of 50, 150, and 500 mg/kg/day. There was an increased incidence of combined liver adenoma/carcinoma in males and females and of liver carcinoma in females at 500 mg/kg. This dose results in exposures approximately 60 times the human exposure at the maximum recommended daily adult human dose (MRHD) of 100 mg/day based on AUC comparisons. Liver tumors were not observed at 150 mg/kg, approximately 20 times the human exposure at the MRHD. A two-year carcinogenicity study was conducted in male and female mice given oral doses of sitagliptin of 50, 125, 250, and 500 mg/kg/day. There was no increase in the incidence of tumors in any organ up to 500 mg/kg, approximately 70 times human exposure at the MRHD. Sitagliptin was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a Chinese hamster ovary (CHO) chromosome aberration assay, an *in vitro* cytogenetics assay in CHO, an *in vitro* rat hepatocyte DNA alkaline elution assay, and an *in vivo* micronucleus assay.

In rat fertility studies with oral gavage doses of 125, 250, and 1000 mg/kg, males were treated for 4 weeks prior to mating, during mating, up to scheduled termination (approximately 8 weeks total), and females were treated 2 weeks prior to mating through gestation day 7. No adverse effect on fertility was observed at 125 mg/kg (approximately 12 times human exposure at the MRHD of 100 mg/day based on AUC comparisons). At higher doses, nondose-related increased resorptions in females were observed (approximately 25 and 100 times human exposure at the MRHD based on AUC comparison).

##### Metformin hydrochloride

Long-term carcinogenicity studies have been performed in Sprague Dawley rats at doses of 150, 300, and 450 mg/kg/day in males and 150, 450, 900, and 1200 mg/kg/day in females. These doses are approximately 2, 4, and 8 times in males, and 3, 7, 12, and 16 times in females of the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female rats. A carcinogenicity study was also performed in Tg.AC transgenic mice at doses up to 2000 mg applied dermally. No evidence of carcinogenicity was observed in male or female mice.

Genotoxicity assessments in the Ames test, gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes) and *in vivo* mouse micronucleus tests were negative. Fertility of male or female rats was not affected by metformin when administered at doses up to 600 mg/kg/day, which is approximately 3 times the maximum recommended human daily dose based on body surface area comparisons.

## 14 CLINICAL STUDIES

The coadministration of sitagliptin and metformin immediate-release has been studied in patients with type 2 diabetes inadequately controlled on diet and exercise and in combination with other antidiabetic medications.

There have been no clinical efficacy or safety studies conducted with JANUMET XR to characterize its effect on hemoglobin A1c (A1C) reduction. Bioequivalence of JANUMET XR tablets with coadministered sitagliptin and extended-release metformin tablets has been demonstrated for all tablet strengths [see *Clinical Pharmacology* (12.3)].

### **Metformin Extended-Release Compared to Metformin Immediate-Release in Patients with Type 2 Diabetes**

In a multicenter, randomized, double-blind, active-controlled, dose-ranging, parallel group trial extended-release metformin 1500 mg once daily, extended-release metformin 1500 mg per day in divided doses (500 mg in the morning and 1000 mg in the evening), and extended-release metformin 2000 mg once daily were compared to immediate-release metformin 1500 mg per day in divided doses (500 mg in the morning and 1000 mg in the evening). This trial enrolled patients (n = 338) who were newly diagnosed with diabetes, patients treated only with diet and exercise, patients treated with a single anti-diabetic medication (sulfonylureas, alpha-glucosidase inhibitors, thiazolidinediones, or meglitinides), and patients (n = 368) receiving metformin up to 1500 mg/day plus a sulfonylurea at a dose equal to or less than one-half the maximum dose. Patients who were enrolled on monotherapy or combination antidiabetic therapy underwent a 6-week washout. Patients randomized to extended-release metformin began titration from 1000 mg/day up to their assigned treatment dose over 3 weeks. Patients randomized to immediate-release metformin initiated 500 mg twice daily for 1 week followed by 500 mg with breakfast and 1000 mg with dinner for the second week. The 3-week treatment period was followed by an additional 21-week period at the randomized dose. For HbA1c and fasting plasma glucose, each of the extended-release metformin regimens was at least as effective as immediate-release metformin. Additionally, once daily dosing of extended-release metformin was as effective as twice daily dosing of the immediate-release metformin formulation.

### **Sitagliptin and Metformin Immediate-Release Coadministration in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise**

A total of 1091 patients with type 2 diabetes and inadequate glycemic control on diet and exercise participated in a 24-week, randomized, double-blind, placebo-controlled factorial study designed to assess the efficacy of sitagliptin and metformin immediate-release coadministration. Patients on an antihyperglycemic agent (N=541) underwent a diet, exercise, and drug washout period of up to 12 weeks duration. After the washout period, patients with inadequate glycemic control (A1C 7.5% to 11%) were randomized after completing a 2-week single-blind placebo run-in period. Patients not on antihyperglycemic agents at study entry (N=550) with inadequate glycemic control (A1C 7.5% to 11%) immediately entered the 2-week single-blind placebo run-in period and then were randomized. Approximately equal numbers of patients were randomized to receive placebo, 100 mg of sitagliptin once daily, 500 mg or 1000 mg of metformin immediate-release twice daily, or 50 mg of sitagliptin twice daily in combination with 500 mg or 1000 mg of metformin immediate-release twice daily. Patients who failed to meet specific glycemic goals during the study were treated with glyburide (glibenclamide) rescue.

Sitagliptin and metformin immediate-release coadministration provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo, to metformin immediate-release alone, and to sitagliptin alone (Table 8, Figure 1). For patients not on an antihyperglycemic agent at study entry, mean reductions from baseline in A1C were: sitagliptin 100 mg once daily, -1.1%; metformin immediate-release 500 mg bid, -1.1%; metformin immediate-release 1000 mg bid, -1.2%; sitagliptin 50 mg bid with metformin immediate-release 500 mg bid, -1.6%; sitagliptin 50 mg bid with metformin immediate-release 1000 mg bid, -1.9%; and for patients receiving placebo, -0.2%. Lipid effects were generally neutral. The decrease in body weight in the groups given sitagliptin in combination with metformin immediate-release was similar to that in the groups given metformin alone or placebo.

**Table 8: Glycemic Parameters at Final Visit (24-Week Study) for Sitagliptin and Metformin Immediate-Release, Alone and in Combination in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise\***

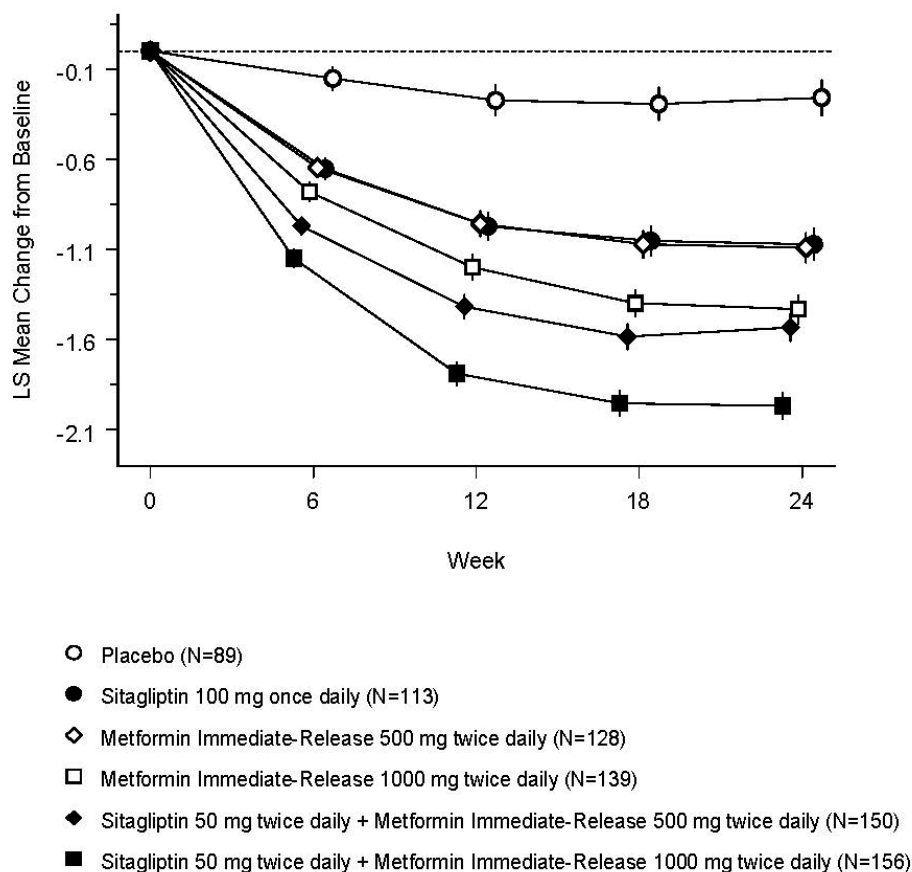
	Placebo	Sitagliptin 100 mg once daily	Metformin Immediate- Release 500 mg twice daily	Metformin Immediate- Release 1000 mg twice daily	Sitagliptin 50 mg bid + Metformin Immediate- Release 500 mg twice daily	Sitagliptin 50 mg bid + Metformin Immediate- Release 1000 mg twice daily
<b>A1C (%)</b>	<b>N = 165</b>	<b>N = 175</b>	<b>N = 178</b>	<b>N = 177</b>	<b>N = 183</b>	<b>N = 178</b>
Baseline (mean)	8.7	8.9	8.9	8.7	8.8	8.8
Change from baseline (adjusted mean <sup>†</sup> )	0.2	-0.7	-0.8	-1.1	-1.4	-1.9
Difference from placebo (adjusted mean <sup>†</sup> ) (95% CI)		-0.8 <sup>‡</sup> (-1.1, -0.6)	-1.0 <sup>‡</sup> (-1.2, -0.8)	-1.3 <sup>‡</sup> (-1.5, -1.1)	-1.6 <sup>‡</sup> (-1.8, -1.3)	-2.1 <sup>‡</sup> (-2.3, -1.8)
Patients (%) achieving A1C <7%	15 (9%)	35 (20%)	41 (23%)	68 (38%)	79 (43%)	118 (66%)
% Patients receiving rescue medication	32	21	17	12	8	2
<b>FPG (mg/dL)</b>	<b>N = 169</b>	<b>N = 178</b>	<b>N = 179</b>	<b>N = 179</b>	<b>N = 183</b>	<b>N = 180</b>
Baseline (mean)	196	201	205	197	204	197
Change from baseline (adjusted mean <sup>†</sup> )	6	-17	-27	-29	-47	-64
Difference from placebo (adjusted mean <sup>†</sup> ) (95% CI)		-23 <sup>‡</sup> (-33, -14)	-33 <sup>‡</sup> (-43, -24)	-35 <sup>‡</sup> (-45, -26)	-53 <sup>‡</sup> (-62, -43)	-70 <sup>‡</sup> (-79, -60)
<b>2-hour PPG (mg/dL)</b>	<b>N = 129</b>	<b>N = 136</b>	<b>N = 141</b>	<b>N = 138</b>	<b>N = 147</b>	<b>N = 152</b>
Baseline (mean)	277	285	293	283	292	287
Change from baseline (adjusted mean <sup>†</sup> )	0	-52	-53	-78	-93	-117
Difference from placebo (adjusted mean <sup>†</sup> ) (95% CI)		-52 <sup>‡</sup> (-67, -37)	-54 <sup>‡</sup> (-69, -39)	-78 <sup>‡</sup> (-93, -63)	-93 <sup>‡</sup> (-107, -78)	-117 <sup>‡</sup> (-131, -102)

\* Intent-to-treat population using last observation on study prior to glyburide (glibenclamide) rescue therapy.

<sup>†</sup> Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.

<sup>‡</sup> p<0.001 compared to placebo.

**Figure 1: Mean Change from Baseline for A1C (%) over 24 Weeks with Sitagliptin and Metformin Immediate-Release, Alone and in Combination in Patients with Type 2 Diabetes Inadequately Controlled with Diet and Exercise\***



\* The Completers Population: least squares means adjusted for prior antihyperglycemic therapy and baseline value.

Initial combination therapy or maintenance of combination therapy should be individualized and are left to the discretion of the health care provider.

#### **Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on Metformin Immediate-Release Alone**

A total of 701 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with metformin immediate-release. Patients already on metformin immediate-release (N=431) at a dose of at least 1500 mg per day were randomized after completing a 2-week, single-blind placebo run-in period. Patients on metformin immediate-release and another antihyperglycemic agent (N=229) and patients not on any antihyperglycemic agents (off therapy for at least 8 weeks, N=41) were randomized after a run-in period of approximately 10 weeks on metformin immediate-release (at a dose of at least 1500 mg per day) in monotherapy. Patients were randomized to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with pioglitazone rescue.

In combination with metformin immediate-release, sitagliptin provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo with metformin immediate-release (Table 9). Rescue glycemic therapy was used in 5% of patients treated with sitagliptin 100 mg and 14% of patients treated with placebo. A similar decrease in body weight was observed for both treatment groups.



**Table 9: Glycemic Parameters at Final Visit (24-Week Study) of Sitagliptin as Add-on Combination Therapy with Metformin Immediate-Release\***

	<b>Sitagliptin 100 mg once daily + Metformin Immediate-Release</b>	<b>Placebo + Metformin Immediate-Release</b>
<b>A1C (%)</b>	<b>N = 453</b>	<b>N = 224</b>
Baseline (mean)	8.0	8.0
Change from baseline (adjusted mean <sup>†</sup> )	-0.7	-0.0
Difference from placebo + metformin immediate-release (adjusted mean <sup>†</sup> ) (95% CI)	-0.7 <sup>‡</sup> (-0.8, -0.5)	
Patients (%) achieving A1C <7%	213 (47%)	41 (18%)
<b>FPG (mg/dL)</b>	<b>N = 454</b>	<b>N = 226</b>
Baseline (mean)	170	174
Change from baseline (adjusted mean <sup>†</sup> )	-17	9
Difference from placebo + metformin immediate-release (adjusted mean <sup>†</sup> ) (95% CI)	-25 <sup>‡</sup> (-31, -20)	
<b>2-hour PPG (mg/dL)</b>	<b>N = 387</b>	<b>N = 182</b>
Baseline (mean)	275	272
Change from baseline (adjusted mean <sup>†</sup> )	-62	-11
Difference from placebo + metformin immediate-release (adjusted mean <sup>†</sup> ) (95% CI)	-51 <sup>‡</sup> (-61, -41)	

\* Intent-to-treat population using last observation on study prior to pioglitazone rescue therapy.

<sup>†</sup> Least squares means adjusted for prior antihyperglycemic therapy and baseline value.

<sup>‡</sup> p<0.001 compared to placebo + metformin.

### **Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on the Combination of Metformin Immediate-Release and Glimepiride**

A total of 441 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with glimepiride, with or without metformin immediate-release. Patients entered a run-in treatment period on glimepiride (≥4 mg per day) alone or glimepiride in combination with metformin immediate-release (≥1500 mg per day). After a dose-titration and dose-stable run-in period of up to 16 weeks and a 2-week placebo run-in period, patients with inadequate glycemic control (A1C 7.5% to 10.5%) were randomized to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with pioglitazone rescue.

Patients receiving sitagliptin with metformin immediate-release and glimepiride had significant improvements in A1C and FPG compared to patients receiving placebo with metformin immediate-release and glimepiride (Table 10), with mean reductions from baseline relative to placebo in A1C of -0.9% and in FPG of -21 mg/dL. Rescue therapy was used in 8% of patients treated with add-on sitagliptin 100 mg and 29% of patients treated with add-on placebo. The patients treated with add-on sitagliptin had a mean increase in body weight of 1.1 kg vs. add-on placebo (+0.4 kg vs. -0.7 kg). In addition, add-on sitagliptin resulted in an increased rate of hypoglycemia compared to add-on placebo. [See *Warnings and Precautions* (5.7); *Adverse Reactions* (6.1).]

**Table 10: Glycemic Parameters at Final Visit (24-Week Study) for Sitagliptin in Combination with Metformin Immediate-Release and Glimepiride\***

	<b>Sitagliptin 100 mg + Metformin Immediate-Release and Glimepiride</b>	<b>Placebo + Metformin Immediate-Release and Glimepiride</b>
<b>A1C (%)</b>	<b>N = 115</b>	<b>N = 105</b>
Baseline (mean)	8.3	8.3
Change from baseline (adjusted mean <sup>†</sup> )	-0.6	0.3
Difference from placebo (adjusted mean <sup>†</sup> ) (95% CI)	-0.9 <sup>‡</sup> (-1.1, -0.7)	
Patients (%) achieving A1C <7%	26 (23%)	1 (1%)
<b>FPG (mg/dL)</b>	<b>N = 115</b>	<b>N = 109</b>
Baseline (mean)	179	179
Change from baseline (adjusted mean <sup>†</sup> )	-8	13
Difference from placebo (adjusted mean <sup>†</sup> ) (95% CI)	-21 <sup>‡</sup> (-32, -10)	

\* Intent-to-treat population using last observation on study prior to pioglitazone rescue therapy.

<sup>†</sup> Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.

<sup>‡</sup> p<0.001 compared to placebo.

### **Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on the Combination of Metformin Immediate-Release and Rosiglitazone**

A total of 278 patients with type 2 diabetes participated in a 54-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with metformin immediate-release and rosiglitazone. Patients on dual therapy with metformin immediate-release ≥1500 mg/day and rosiglitazone ≥4 mg/day or with metformin immediate-release ≥1500 mg/day and pioglitazone ≥30 mg/day (switched to rosiglitazone ≥4 mg/day) entered a dose-stable run-in period of 6 weeks. Patients on other dual therapy were switched to metformin immediate-release ≥1500 mg/day and rosiglitazone ≥4 mg/day in a dose titration/stabilization run-in period of up to 20 weeks in duration. After the run-in period, patients with inadequate glycemic control (A1C 7.5% to 11%) were randomized 2:1 to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with glipizide (or other sulfonylurea) rescue. The primary time point for evaluation of glycemic parameters was Week 18.

In combination with metformin immediate-release and rosiglitazone, sitagliptin provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo with metformin immediate-release and rosiglitazone (Table 11) at Week 18. At Week 54, mean reduction in A1C was -1.0% for patients treated with sitagliptin and -0.3% for patients treated with placebo in an analysis based on the intent-to-treat population. Rescue therapy was used in 18% of patients treated with sitagliptin 100 mg and 40% of patients treated with placebo. There was no significant difference between sitagliptin and placebo in body weight change.

**Table 11: Glycemic Parameters at Week 18 for Sitagliptin in Add-on Combination Therapy with Metformin Immediate-Release and Rosiglitazone\***

	Week 18	
	Sitagliptin 100 mg + Metformin Immediate-Release + Rosiglitazone	Placebo + Metformin Immediate-Release + Rosiglitazone
<b>A1C (%)</b>	<b>N = 176</b>	<b>N = 93</b>
Baseline (mean)	8.8	8.7
Change from baseline (adjusted mean†)	-1.0	-0.4
Difference from placebo + rosiglitazone + metformin immediate-release (adjusted mean†) (95% CI)	-0.7‡ (-0.9, -0.4)	
Patients (%) achieving A1C <7%	39 (22%)	9 (10%)
<b>FPG (mg/dL)</b>	<b>N = 179</b>	<b>N = 94</b>
Baseline (mean)	181	182
Change from baseline (adjusted mean†)	-30	-11
Difference from placebo + rosiglitazone + metformin immediate-release (adjusted mean†) (95% CI)	-18‡ (-26, -10)	
<b>2-hour PPG (mg/dL)</b>	<b>N = 152</b>	<b>N = 80</b>
Baseline (mean)	256	248
Change from baseline (adjusted mean†)	-59	-21
Difference from placebo + rosiglitazone + metformin immediate-release (adjusted mean†) (95% CI)	-39‡ (-51, -26)	

\* Intent-to-treat population using last observation on study prior to glipizide (or other sulfonylurea) rescue therapy.

† Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.

‡ p<0.001 compared to placebo + metformin + rosiglitazone.

### **Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on the Combination of Metformin Immediate-Release and Insulin**

A total of 641 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin as add-on to insulin therapy. Approximately 75% of patients were also taking metformin immediate-release. Patients entered a 2-week, single-blind run-in treatment period on pre-mixed, long-acting, or intermediate-acting insulin, with or without metformin immediate-release ( $\geq 1500$  mg per day). Patients using short-acting insulins were excluded unless the short-acting insulin was administered as part of a pre-mixed insulin. After the run-in period, patients with inadequate glycemic control (A1C 7.5% to 11%) were randomized to the addition of either 100 mg of sitagliptin (N=229) or placebo (N=233), administered once daily. Patients were on a stable dose of insulin prior to enrollment with no changes in insulin dose permitted during the run-in period. Patients who failed to meet specific glycemic goals during the double-blind treatment period were to have uptitration of the background insulin dose as rescue therapy.

Among patients also receiving metformin immediate-release, the median daily insulin (pre-mixed, intermediate or long acting) dose at baseline was 40 units in the sitagliptin-treated patients and 42 units in the placebo-treated patients. The median change from baseline in daily dose of insulin was zero for both groups at the end of the study. Patients receiving sitagliptin with metformin immediate-release and insulin

had significant improvements in A1C, FPG and 2-hour PPG compared to patients receiving placebo with metformin immediate-release and insulin (Table 12). The adjusted mean change from baseline in body weight was -0.3 kg in patients receiving sitagliptin with metformin immediate-release and insulin and -0.2 kg in patients receiving placebo with metformin immediate-release and insulin. There was an increased rate of hypoglycemia in patients treated with sitagliptin. [See *Warnings and Precautions* (5.7); *Adverse Reactions* (6.1).]

**Table 12: Glycemic Parameters at Final Visit (24-Week Study) for Sitagliptin as Add-on Combination Therapy with Metformin Immediate-Release and Insulin\***

	Sitagliptin 100 mg + Metformin Immediate- Release + Insulin	Placebo + Metformin Immediate- Release + Insulin
<b>A1C (%)</b>	<b>N = 223</b>	<b>N = 229</b>
Baseline (mean)	8.7	8.6
Change from baseline (adjusted mean <sup>†</sup> , ‡)	-0.7	-0.1
Difference from placebo (adjusted mean <sup>†</sup> ) (95% CI)	-0.5 <sup>§</sup> (-0.7, -0.4)	
Patients (%) achieving A1C <7%	32 (14%)	12 (5%)
<b>FPG (mg/dL)</b>	<b>N = 225</b>	<b>N = 229</b>
Baseline (mean)	173	176
Change from baseline (adjusted mean <sup>†</sup> )	-22	-4
Difference from placebo (adjusted mean <sup>†</sup> ) (95% CI)	-18 <sup>§</sup> (-28, -8.4)	
<b>2-hour PPG (mg/dL)</b>	<b>N = 182</b>	<b>N = 189</b>
Baseline (mean)	281	281
Change from baseline (adjusted mean <sup>†</sup> )	-39	1
Difference from placebo (adjusted mean <sup>†</sup> ) (95% CI)	-40 <sup>§</sup> (-53, -28)	

\* Intent-to-treat population using last observation on study prior to rescue therapy.

<sup>†</sup> Least squares means adjusted for insulin use at the screening visit, type of insulin used at the screening visit (pre-mixed vs. non pre-mixed [intermediate- or long-acting]), and baseline value.

<sup>‡</sup> Treatment by insulin stratum interaction was not significant (p>0.10).

<sup>§</sup> p<0.001 compared to placebo.

### **Sitagliptin Add-on Therapy vs. Glipizide Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on Metformin Immediate-Release**

The efficacy of sitagliptin was evaluated in a 52-week, double-blind, glipizide-controlled noninferiority trial in patients with type 2 diabetes. Patients not on treatment or on other antihyperglycemic agents entered a run-in treatment period of up to 12 weeks duration with metformin immediate-release monotherapy (dose of ≥1500 mg per day) which included washout of medications other than metformin immediate-release, if applicable. After the run-in period, those with inadequate glycemic control (A1C 6.5% to 10%) were randomized 1:1 to the addition of sitagliptin 100 mg once daily or glipizide for 52 weeks. Patients receiving glipizide were given an initial dosage of 5 mg/day and then electively titrated over the next 18 weeks to a maximum dosage of 20 mg/day as needed to optimize glycemic control. Thereafter, the glipizide dose was to be kept constant, except for down-titration to prevent hypoglycemia. The mean dose of glipizide after the titration period was 10 mg.

After 52 weeks, sitagliptin and glipizide had similar mean reductions from baseline in A1C in the intent-to-treat analysis (Table 13). These results were consistent with the per protocol analysis (Figure 2). A conclusion in favor of the non-inferiority of sitagliptin to glipizide may be limited to patients with baseline A1C comparable to those included in the study (over 70% of patients had baseline A1C <8% and over 90% had A1C <9%).

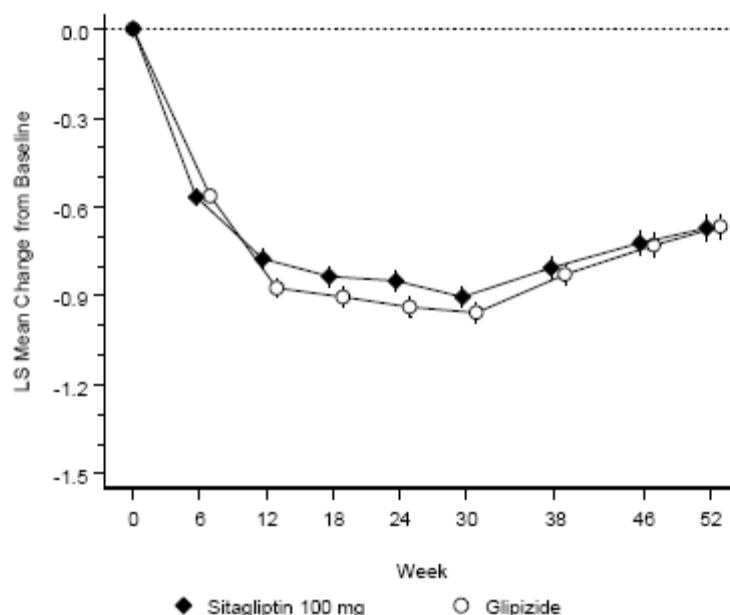
**Table 13: Glycemic Parameters in a 52-Week Study Comparing Sitagliptin to Glipizide as Add-On Therapy in Patients Inadequately Controlled on Metformin Immediate-Release (Intent-to-Treat Population) \***

	Sitagliptin 100 mg + Metformin Immediate-Release	Glipizide + Metformin Immediate-Release
<b>A1C (%)</b>	<b>N = 576</b>	<b>N = 559</b>
Baseline (mean)	7.7	7.6
Change from baseline (adjusted mean <sup>†</sup> )	-0.5	-0.6
<b>FPG (mg/dL)</b>	<b>N = 583</b>	<b>N = 568</b>
Baseline (mean)	166	164
Change from baseline (adjusted mean <sup>†</sup> )	-8	-8

\* The intent-to-treat analysis used the patients' last observation in the study prior to discontinuation.

<sup>†</sup> Least squares means adjusted for prior antihyperglycemic therapy status and baseline A1C value.

**Figure 2: Mean Change from Baseline for A1C (%) Over 52 Weeks in a Study Comparing Sitagliptin to Glipizide as Add-On Therapy in Patients Inadequately Controlled on Metformin Immediate-Release (Per Protocol Population)\***



\* The per protocol population (mean baseline A1C of 7.5%) included patients without major protocol violations who had observations at baseline and at Week 52.

The incidence of hypoglycemia in the sitagliptin group (4.9%) was significantly ( $p < 0.001$ ) lower than that in the glipizide group (32.0%). Patients treated with sitagliptin exhibited a significant mean decrease from baseline in body weight compared to a significant weight gain in patients administered glipizide (-1.5 kg vs. +1.1 kg).

## 16 HOW SUPPLIED/STORAGE AND HANDLING

No. 3961 — Tablets JANUMET XR, 50 mg/500 mg, are light blue, bi-convex oval, film-coated tablets with “78” debossed on one side. They are supplied as follows:

NDC 0006-0078-61 unit-of-use bottles of 60  
NDC 0006-0078-62 unit-of-use bottles of 180  
NDC 0006-0078-82 bulk bottles of 1000.

No. 3962 — Tablets JANUMET XR, 50 mg/1000 mg, are light green, bi-convex oval, film-coated tablets with “80” debossed on one side. They are supplied as follows:

NDC 0006-0080-61 unit-of-use bottles of 60  
NDC 0006-0080-62 unit-of-use bottles of 180  
NDC 0006-0080-82 bulk bottles of 1000.

No. 3963 — Tablets JANUMET XR, 100 mg/1000 mg, are blue, bi-convex oval, film-coated tablets with “81” debossed on one side. They are supplied as follows:

NDC 0006-0081-31 unit-of-use bottles of 30  
NDC 0006-0081-54 unit-of-use bottles of 90  
NDC 0006-0081-82 bulk bottles of 1000.

Store at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.] Store in a dry place with cap tightly closed. When container is subdivided, dispense into a USP tightly closed, moisture-resistant container.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

### 17.1 Instructions

Patients should be informed of the potential risks and benefits of JANUMET XR and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and A1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be advised to seek medical advice promptly.

The risks of lactic acidosis due to the metformin component, its symptoms, and conditions that predispose to its development, as noted in Warnings and Precautions (5.1), should be explained to patients. Patients should be advised to discontinue JANUMET XR immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence, dizziness, slow or irregular heart beat, sensation of feeling cold (especially in the extremities) or other nonspecific symptoms occur. Gastrointestinal symptoms are common during initiation of metformin treatment and may occur during initiation of JANUMET XR therapy; however, patients should consult their physician if they develop unexplained symptoms. Although gastrointestinal symptoms that occur after stabilization are unlikely to be drug related, such an occurrence of symptoms should be evaluated to determine if it may be due to lactic acidosis or other serious disease. Instruct patients to inform their doctor that they are taking JANUMET XR prior to any surgical or radiological procedure, as temporary discontinuation of JANUMET XR may be required until renal function has been confirmed to have returned to its prior level [see Warnings and Precautions (5.1)].

Patients should be advised to notify their health practitioner or call the Poison Control Center immediately in case of JANUMET XR overdose.

Patients should be counseled against excessive alcohol intake, either acute or chronic, while receiving JANUMET XR.

Patients should be informed about the importance of regular testing of renal function and hematological parameters when receiving treatment with JANUMET XR.

Patients should be informed that acute pancreatitis has been reported during postmarketing use of JANUMET. Patients should be informed that persistent severe abdominal pain, sometimes radiating to the

back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Patients should be instructed to promptly discontinue JANUMET XR and contact their physician if persistent severe abdominal pain occurs [see *Warnings and Precautions* (5.2)].

Patients should be informed of the signs and symptoms of heart failure. Before initiating JANUMET XR, patients should be asked about a history of heart failure or other risk factors for heart failure including moderate to severe renal impairment. Patients should be instructed to contact their health care provider as soon as possible if they experience symptoms of heart failure, including increasing shortness of breath, rapid increase in weight or swelling of the feet [see *Warnings and Precautions* (5.3)].

Patients should be informed that the incidence of hypoglycemia is increased when sitagliptin with or without metformin is added to an insulin secretagogue (e.g., sulfonylurea) or insulin therapy and that a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia.

Patients should be informed that allergic reactions have been reported during postmarketing use of sitagliptin, one of the components of JANUMET XR. If symptoms of allergic reactions (including rash, hives, and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing) occur, patients must stop taking JANUMET XR and seek medical advice promptly.

Inform patients that severe and disabling joint pain may occur with this class of drugs. The time to onset of symptoms can range from one day to years. Instruct patients to seek medical advice if severe joint pain occurs [see *Warnings and Precautions* (5.10)].

Inform patients that bullous pemphigoid may occur with this class of drugs. Instruct patients to seek medical advice if blisters or erosions occur [see *Warnings and Precautions* (5.11)].

Patients should be informed that the tablets must be swallowed whole and never split, crushed or chewed.

Patients should be informed that incompletely dissolved JANUMET XR tablets may be eliminated in the feces. Tell patients that, if they repeatedly see tablets in feces, they should report this finding to their health care provider. If a patient reports repeatedly observing tablets in feces, the health care provider should assess adequacy of glycemic control.

Physicians should instruct their patients to read the Medication Guide before starting JANUMET XR therapy and to reread each time the prescription is renewed. Patients should be instructed to inform their doctor if they develop any bothersome or unusual symptom, or if any symptom persists or worsens.

## **17.2 Laboratory Tests**

Response to all diabetic therapies should be monitored by periodic measurements of blood glucose and A1C levels, with a goal of decreasing these levels towards the normal range. A1C is especially useful for evaluating long-term glycemic control.

Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with metformin therapy, if this is suspected, Vitamin B<sub>12</sub> deficiency should be excluded.

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**Medication Guide**  
**JANUMET® XR (JAN-you-met XR)**  
**(sitagliptin and metformin hydrochloride extended-release)**  
**Tablets**

Read this Medication Guide carefully before you start taking JANUMET XR and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about JANUMET XR, ask your doctor or pharmacist.

**What is the most important information I should know about JANUMET XR?**

**Serious side effects can happen in people taking JANUMET XR, including:**

- 1. Lactic Acidosis.** Metformin, one of the medicines in JANUMET XR, can cause a rare but serious condition called lactic acidosis (a buildup of an acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in the hospital.

Call your doctor right away if you have any of the following symptoms, which could be signs of lactic acidosis:

- you feel cold in your hands or feet
- you feel dizzy or lightheaded
- you have a slow or irregular heartbeat
- you feel very weak or tired
- you have unusual (not normal) muscle pain
- you have trouble breathing
- you feel sleepy or drowsy
- you have stomach pains, nausea or vomiting

Most people who have had lactic acidosis with metformin have other things that, combined with the metformin, led to the lactic acidosis. Tell your doctor if you have any of the following, because you have a higher chance for getting lactic acidosis with JANUMET XR if you:

- have severe kidney problems or your kidneys are affected by certain x-ray tests that use injectable dye
- have liver problems
- drink alcohol very often, or drink a lot of alcohol in short-term "binge" drinking
- get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids
- have surgery
- have a heart attack, severe infection, or stroke

The best way to keep from having a problem with lactic acidosis from metformin is to tell your doctor if you have any of the problems in the list above. Your doctor may decide to stop your JANUMET XR for a while if you have any of these things.

JANUMET XR can have other serious side effects. See **"What are the possible side effects of JANUMET XR?"**

- 2. Pancreatitis** (inflammation of the pancreas) which may be severe and lead to death.

Certain medical problems make you more likely to get pancreatitis.

**Before you start taking JANUMET XR:**

Tell your doctor if you have ever had

- pancreatitis
- stones in your gallbladder (gallstones)
- a history of alcoholism
- high blood triglyceride levels

Stop taking JANUMET XR and call your doctor right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen through to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

- 3. Heart failure.** Heart failure means that your heart does not pump blood well enough.

**Before you start taking JANUMET XR,** tell your doctor if you have ever had heart failure or have problems with your kidneys. Contact your doctor right away if you have any of the following symptoms:

- increasing shortness of breath or trouble breathing, especially when you lie down
- swelling or fluid retention, especially in the feet, ankles or legs
- an unusually fast increase in weight
- unusual tiredness



These may be symptoms of heart failure.

**What is JANUMET XR?**

- JANUMET XR is a prescription medicine that contains 2 prescription diabetes medicines, sitagliptin (JANUVIA®) and extended-release metformin hydrochloride. JANUMET XR can be used along with diet and exercise to lower blood sugar in adults with type 2 diabetes.
- JANUMET XR is not for people with type 1 diabetes.
- JANUMET XR is not for people with diabetic ketoacidosis (increased ketones in your blood or urine).
- If you have had pancreatitis (inflammation of the pancreas) in the past, it is not known if you have a higher chance of getting pancreatitis while you take JANUMET XR.
- It is not known if JANUMET XR is safe and effective when used in children under 18 years of age.

**Who should not take JANUMET XR?**

**Do not take JANUMET XR if:**

- you have severe kidney problems.
- you are allergic to any of the ingredients in JANUMET XR. See the end of this Medication Guide for a complete list of ingredients in JANUMET XR.

Symptoms of a serious allergic reaction to JANUMET XR may include rash, raised red patches on your skin (hives) or swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing.

- you have diabetic ketoacidosis. See "**What is JANUMET XR?**".

**What should I tell my doctor before taking JANUMET XR?**

**Before you take JANUMET XR, tell your doctor if you:**

- have or have had inflammation of your pancreas (pancreatitis).
  - have severe kidney problems.
  - have liver problems.
  - have heart problems, including congestive heart failure.
  - drink alcohol very often, or drink a lot of alcohol in short-term "binge" drinking.
  - are going to get an injection of dye or contrast agents for an x-ray procedure; JANUMET XR may need to be stopped for a short time. Talk to your doctor about when you should stop JANUMET XR and when you should start JANUMET XR again. See "**What is the most important information I should know about JANUMET XR?**".
  - have any other medical conditions.
  - are pregnant or plan to become pregnant. It is not known if JANUMET XR will harm your unborn baby. If you are pregnant, talk with your doctor about the best way to control your blood sugar while you are pregnant.
- Pregnancy Registry:** If you take JANUMET XR at any time during your pregnancy, talk with your doctor about how you can join the JANUMET XR pregnancy registry. The purpose of this registry is to collect information about the health of you and your baby. You can enroll in this registry by calling 1-800-986-8999.
- are breast-feeding or plan to breast-feed. It is not known if JANUMET XR will pass into your breast milk. Talk with your doctor about the best way to feed your baby if you are taking JANUMET XR.

**Tell your doctor about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements. JANUMET XR may affect how well other drugs work and some drugs can affect how well JANUMET XR works.

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine.

**How should I take JANUMET XR?**

- Take JANUMET XR exactly as your doctor tells you. Your doctor will tell you how many JANUMET XR tablets to take and when you should take them.
- Your doctor may change your dose of JANUMET XR if needed.
- Your doctor may tell you to take JANUMET XR along with certain other diabetes medicines. Low blood sugar (hypoglycemia) can happen more often when JANUMET XR is taken with certain other diabetes medicines. See "**What are the possible side effects of JANUMET XR?**".
- Take JANUMET XR 1 time each day with a meal to help to lower your chance of having an upset stomach. It is better to take JANUMET XR with your evening meal.
- Take JANUMET XR tablets whole. Do not break, cut, crush, dissolve, or chew JANUMET XR tablets before swallowing. If you cannot swallow JANUMET XR tablets whole, tell your doctor.
- You may see something that looks like the JANUMET XR tablet in your stool (bowel movement). If you see tablets in your stool several times, talk to your doctor. Do not stop taking JANUMET XR without talking to your doctor.

- Continue to take JANUMET XR as long as your doctor tells you.
- If you take too much JANUMET XR, call your doctor or local Poison Control Center right away.
- If you miss a dose, take it with food as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take 2 doses of JANUMET XR at the same time.
- You may need to stop taking JANUMET XR for a short time. Call your doctor for instructions if you:
  - are dehydrated (have lost too much body fluid). Dehydration can occur if you are sick with severe vomiting, diarrhea or fever, or if you drink a lot less fluid than normal.
  - plan to have surgery.
  - are going to get an injection of dye or contrast agent for an x-ray procedure. See **"What is the most important information I should know about JANUMET XR?"** and **"What should I tell my doctor before taking JANUMET XR?"**.
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection or surgery, the amount of diabetes medicine that you need may change. Tell your doctor right away if you have any of these problems and follow your doctor's instructions.
- Check your blood sugar as your doctor tells you to.
- Stay on your prescribed diet and exercise program while taking JANUMET XR.
- Talk to your doctor about how to prevent, recognize and manage low blood sugar (hypoglycemia), high blood sugar (hyperglycemia), and problems you have because of your diabetes.
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1C.
- Your doctor will do blood tests to check how well your kidneys are working before and during your treatment with JANUMET XR.

#### **What are the possible side effects of JANUMET XR?**

**Serious side effects have happened in people taking JANUMET XR or the individual medicines in JANUMET XR.**

- See **"What is the most important information I should know about JANUMET XR?"**.
- **Low blood sugar (hypoglycemia).** If you take JANUMET XR with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you use JANUMET XR. Signs and symptoms of low blood sugar may include:
 

• headache	• irritability	• dizziness	• sweating	• weakness
• drowsiness	• hunger	• confusion	• feeling jittery	• fast heart beat
- **Serious allergic reactions.** If you have any symptoms of a serious allergic reaction, stop taking JANUMET XR and call your doctor right away. See **"Who should not take JANUMET XR?"**. Your doctor may give you a medicine for your allergic reaction and prescribe a different medicine for your diabetes.
- **Kidney problems,** sometimes requiring dialysis.
- **Joint pain.** Some people who take medicines called DPP-4 inhibitors, one of the medicines in JANUMET XR, may develop joint pain that can be severe. Call your doctor if you have severe joint pain.
- **Skin reaction.** Some people who take medicines called DPP-4 inhibitors, one of the medicines in JANUMET XR, may develop a skin reaction called bullous pemphigoid that can require treatment in a hospital. Tell your doctor right away if you develop blisters or the breakdown of the outer layer of your skin (erosion). Your doctor may tell you to stop taking JANUMET XR.

The most common side effects of JANUMET XR include:

- |  |                               |  |
|--|-------------------------------|--|
| • stuffy or runny nose and sore throat | • upper respiratory infection | • low blood sugar (hypoglycemia) when used in combination with certain medications, such as a sulfonylurea or insulin. |
| • gas, upset stomach, indigestion      | • weakness                    | • nausea and vomiting  |
| • headache                             | • diarrhea                    |  |

Taking JANUMET XR with meals can help lessen the common stomach side effects of metformin that usually happen at the beginning of treatment. If you have unusual or sudden stomach problems, talk with your doctor. Stomach problems that start later during treatment may be a sign of something more serious.

**JANUMET XR may have other side effects, including swelling of the hands or legs.** Swelling of the hands and legs can happen if you take JANUMET XR in combination with rosiglitazone (Avandia®). Rosiglitazone is another type of diabetes medicine.

These are not all the possible side effects of JANUMET XR. For more information, ask your doctor or pharmacist.

Tell your doctor if you have any side effect that bothers you, is unusual, or does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store JANUMET XR?**

Store JANUMET XR at 68°F to 77°F (20°C to 25°C). Store in a dry place and keep cap tightly closed.

**Keep JANUMET XR and all medicines out of the reach of children.**

**General information about the use of JANUMET XR.**

Medicines are sometimes prescribed for purposes other than those listed in Medication Guides. Do not use JANUMET XR for a condition for which it was not prescribed. Do not give JANUMET XR to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about JANUMET XR. If you would like to know more information, talk with your doctor. You can ask your doctor or pharmacist for additional information about JANUMET XR that is written for health care professionals. For more information go to [www.janumetxr.com](http://www.janumetxr.com) or call 1-800-622-4477.

**What are the ingredients in JANUMET XR?**

**Active ingredients:** sitagliptin and metformin hydrochloride extended-release

**Inactive ingredients:**

- **All doses of JANUMET XR Tablets contain:** povidone, hypromellose, colloidal silicon dioxide, sodium stearyl fumarate, propyl gallate, polyethylene glycol, and kaolin. Film coating contains hypromellose, hydroxypropyl cellulose, titanium dioxide, FD&C #2/Indigo Carmine Aluminum Lake and carnauba wax.
- **In addition the JANUMET XR 50 mg/500 mg Tablets also contain:** microcrystalline cellulose.
- **In addition the JANUMET XR 50 mg/1000 mg Tablets also contain:** yellow iron oxide.

**What is type 2 diabetes?**

Type 2 diabetes is a condition in which your body does not make enough insulin, and the insulin that your body produces does not work as well as it should. Your body can also make too much sugar. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems.

High blood sugar can be lowered by diet and exercise, and by certain medicines when necessary.

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: XX/20XX