

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

### JANUVIA® (sitagliptin) Tablets

Initial U.S. Approval: 2006

#### RECENT MAJOR CHANGES

##### Warnings and Precautions

Severe and Disabling Arthralgia (5.5) 08/2015

#### INDICATIONS AND USAGE

JANUVIA is a dipeptidyl peptidase-4 (DPP-4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1.1)

##### Important Limitations of Use:

- JANUVIA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. (1.2)
- JANUVIA has not been studied in patients with a history of pancreatitis. (1.2, 5.1)

#### DOSAGE AND ADMINISTRATION

The recommended dose of JANUVIA is 100 mg once daily. JANUVIA can be taken with or without food. (2.1)

Dosage adjustment is recommended for patients with moderate or severe renal insufficiency or end-stage renal disease. (2.2)

Dosage Adjustment in Patients With Moderate, Severe and End Stage Renal Disease (ESRD) (2.2)	
50 mg once daily	25 mg once daily
Moderate	Severe and ESRD
CrCl $\geq$ 30 to $<$ 50 mL/min ~Serum Cr levels [mg/dL] Men: $>$ 1.7– $\leq$ 3.0; Women: $>$ 1.5– $\leq$ 2.5	CrCl $<$ 30 mL/min ~Serum Cr levels [mg/dL] Men: $>$ 3.0; Women: $>$ 2.5; or on dialysis

#### DOSAGE FORMS AND STRENGTHS

Tablets: 100 mg, 50 mg, and 25 mg (3)

#### CONTRAINDICATIONS

History of a serious hypersensitivity reaction to sitagliptin, such as anaphylaxis or angioedema (5.4, 6.2)

#### WARNINGS AND PRECAUTIONS

- There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. If pancreatitis is suspected, promptly discontinue JANUVIA. (5.1)
- There have been postmarketing reports of acute renal failure, sometimes requiring dialysis. Dosage adjustment is recommended in patients with moderate or severe renal insufficiency and in patients with ESRD. Assessment of renal function is recommended prior to initiating JANUVIA and periodically thereafter. (2.2, 5.2, 6.2)
- There is an increased risk of hypoglycemia when JANUVIA is added to an insulin secretagogue (e.g., sulfonylurea) or insulin therapy. Consider lowering the dose of the sulfonylurea or insulin to reduce the risk of hypoglycemia. (2.3, 5.3)
- There have been postmarketing reports of serious allergic and hypersensitivity reactions in patients treated with JANUVIA such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. In such cases, promptly stop JANUVIA, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes. (5.4, 6.2)
- 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. (5.5)
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with JANUVIA or any other anti-diabetic drug. (5.6)

#### ADVERSE REACTIONS

Adverse reactions reported in  $\geq$ 5% of patients treated with JANUVIA and more commonly than in patients treated with placebo are: upper respiratory tract infection, nasopharyngitis and headache. In the add-on to sulfonylurea and add-on to insulin studies, hypoglycemia was also more commonly reported in patients treated with JANUVIA compared to placebo. (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).

#### USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/2015

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 Monotherapy and Combination Therapy

JANUVIA<sup>®</sup> is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. [See *Clinical Studies (14).*]

#### 1.2 Important Limitations of Use

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

JANUVIA 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 JANUVIA. [See *Warnings and Precautions (5.1).*]

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Recommended Dosing

The recommended dose of JANUVIA is 100 mg once daily. JANUVIA can be taken with or without food.

#### 2.2 Patients with Renal Insufficiency

For patients with mild renal insufficiency (creatinine clearance [CrCl] greater than or equal to 50 mL/min, approximately corresponding to serum creatinine levels of less than or equal to 1.7 mg/dL in men and less than or equal to 1.5 mg/dL in women), no dosage adjustment for JANUVIA is required.

For patients with moderate renal insufficiency (CrCl greater than or equal to 30 to less than 50 mL/min, approximately corresponding to serum creatinine levels of greater than 1.7 to less than or equal to 3.0 mg/dL in men and greater than 1.5 to less than or equal to 2.5 mg/dL in women), the dose of JANUVIA is 50 mg once daily.

For patients with severe renal insufficiency (CrCl less than 30 mL/min, approximately corresponding to serum creatinine levels of greater than 3.0 mg/dL in men and greater than 2.5 mg/dL in women) or with end-stage renal disease (ESRD) requiring hemodialysis or peritoneal dialysis, the dose of JANUVIA is 25 mg once daily. JANUVIA may be administered without regard to the timing of dialysis.

Because there is a need for dosage adjustment based upon renal function, assessment of renal function is recommended prior to initiation of JANUVIA and periodically thereafter. Creatinine clearance can be estimated from serum creatinine using the Cockcroft-Gault formula. [See *Clinical Pharmacology (12.3).*] There have been postmarketing reports of worsening renal function in patients with renal insufficiency, some of whom were prescribed inappropriate doses of sitagliptin.

#### 2.3 Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin

When JANUVIA is used in combination with an insulin secretagogue (e.g., sulfonylurea) or with insulin, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia. [See *Warnings and Precautions (5.3).*]

### 3 DOSAGE FORMS AND STRENGTHS

- 100 mg tablets are beige, round, film-coated tablets with “277” on one side.
- 50 mg tablets are light beige, round, film-coated tablets with “112” on one side.
- 25 mg tablets are pink, round, film-coated tablets with “221” on one side.

### 4 CONTRAINDICATIONS

History of a serious hypersensitivity reaction to sitagliptin, such as anaphylaxis or angioedema. [See *Warnings and Precautions (5.4); Adverse Reactions (6.2).*]

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Pancreatitis

There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking JANUVIA. After initiation of JANUVIA, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, JANUVIA 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 JANUVIA.

## **5.2 Renal Impairment**

Assessment of renal function is recommended prior to initiating JANUVIA and periodically thereafter. A dosage adjustment is recommended in patients with moderate or severe renal insufficiency and in patients with ESRD requiring hemodialysis or peritoneal dialysis. [See *Dosage and Administration (2.2)*; *Clinical Pharmacology (12.3)*.] Caution should be used to ensure that the correct dose of JANUVIA is prescribed for patients with moderate (creatinine clearance  $\geq 30$  to  $< 50$  mL/min) or severe (creatinine clearance  $< 30$  mL/min) renal impairment.

There have been postmarketing reports of worsening renal function, including acute renal failure, sometimes requiring dialysis. A subset of these reports involved patients with renal insufficiency, some of whom were prescribed inappropriate doses of sitagliptin. A return to baseline levels of renal insufficiency has been observed with supportive treatment and discontinuation of potentially causative agents. Consideration can be given to cautiously reinitiating JANUVIA if another etiology is deemed likely to have precipitated the acute worsening of renal function.

JANUVIA has not been found to be nephrotoxic in preclinical studies at clinically relevant doses, or in clinical trials.

## **5.3 Use with Medications Known to Cause Hypoglycemia**

When JANUVIA 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 (6.1)*.] Therefore, a lower dose of sulfonylurea or insulin may be required to reduce the risk of hypoglycemia. [See *Dosage and Administration (2.3)*.]

## **5.4 Hypersensitivity Reactions**

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with JANUVIA. 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 JANUVIA, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue JANUVIA, assess for other potential causes for the event, and institute alternative treatment for diabetes. [See *Adverse Reactions (6.2)*.]

Angioedema has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors. Use caution in a patient with a history of angioedema with another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with JANUVIA.

## **5.5 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.

## **5.6 Macrovascular Outcomes**

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with JANUVIA or any other anti-diabetic drug.

# **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.

In controlled clinical studies as both monotherapy and combination therapy with metformin, pioglitazone, or rosiglitazone and metformin, the overall incidence of adverse reactions, hypoglycemia, and discontinuation of therapy due to clinical adverse reactions with JANUVIA were similar to placebo. In combination with glimepiride, with or without metformin, the overall incidence of clinical adverse reactions with JANUVIA was higher than with placebo, in part related to a higher incidence of hypoglycemia (see Table 3); the incidence of discontinuation due to clinical adverse reactions was similar to placebo.

Two placebo-controlled monotherapy studies, one of 18- and one of 24-week duration, included patients treated with JANUVIA 100 mg daily, JANUVIA 200 mg daily, and placebo. Five placebo-controlled add-on combination therapy studies were also conducted: one with metformin; one with pioglitazone; one with metformin and rosiglitazone; one with glimepiride (with or without metformin); and one with insulin (with or without metformin). In these trials, patients with inadequate glycemic control on a stable dose of the background therapy were randomized to add-on therapy with JANUVIA 100 mg daily or placebo. The adverse reactions, excluding hypoglycemia, reported regardless of investigator assessment of causality in  $\geq 5\%$  of patients treated with JANUVIA 100 mg daily and more commonly than in patients treated with placebo, are shown in Table 1 for the clinical trials of at least 18 weeks duration. Incidences of hypoglycemia are shown in Table 3.

**Table 1:**  
**Placebo-Controlled Clinical Studies of JANUVIA Monotherapy or Add-on Combination Therapy with Pioglitazone, Metformin + Rosiglitazone, or Glimepiride +/- Metformin: Adverse Reactions (Excluding Hypoglycemia) Reported in  $\geq 5\%$  of Patients and More Commonly than in Patients Given Placebo, Regardless of Investigator Assessment of Causality\***

Monotherapy (18 or 24 weeks)	Number of Patients (%)	
	JANUVIA 100 mg	Placebo
	N = 443	N = 363
Nasopharyngitis	23 (5.2)	12 (3.3)
Combination with Pioglitazone (24 weeks)	JANUVIA 100 mg + Pioglitazone	Placebo + Pioglitazone
	N = 175	N = 178
Upper Respiratory Tract Infection	11 (6.3)	6 (3.4)
Headache	9 (5.1)	7 (3.9)
Combination with Metformin + Rosiglitazone (18 weeks)	JANUVIA 100 mg + Metformin + Rosiglitazone	Placebo + Metformin + Rosiglitazone
	N = 181	N = 97
Upper Respiratory Tract Infection	10 (5.5)	5 (5.2)
Nasopharyngitis	11 (6.1)	4 (4.1)
Combination with Glimepiride (+/- Metformin) (24 weeks)	JANUVIA 100 mg + Glimepiride (+/- Metformin)	Placebo + Glimepiride (+/- Metformin)
	N = 222	N = 219
Nasopharyngitis	14 (6.3)	10 (4.6)
Headache	13 (5.9)	5 (2.3)

\* Intent-to-treat population

In the 24-week study of patients receiving JANUVIA as add-on combination therapy with metformin, there were no adverse reactions reported regardless of investigator assessment of causality in  $\geq 5\%$  of patients and more commonly than in patients given placebo.

In the 24-week study of patients receiving JANUVIA as add-on therapy to insulin (with or without metformin), there were no adverse reactions reported regardless of investigator assessment of causality in  $\geq 5\%$  of patients and more commonly than in patients given placebo, except for hypoglycemia (see Table 3).

In the study of JANUVIA as add-on combination therapy with metformin and rosiglitazone (Table 1), through Week 54 the adverse reactions reported regardless of investigator assessment of causality in  $\geq 5\%$  of patients treated with JANUVIA and more commonly than in patients treated with placebo were: upper respiratory tract infection (JANUVIA, 15.5%; placebo, 6.2%), nasopharyngitis (11.0%, 9.3%), peripheral edema (8.3%, 5.2%), and headache (5.5%, 4.1%).

In a pooled analysis of the two monotherapy studies, the add-on to metformin study, and the add-on to pioglitazone study, the incidence of selected gastrointestinal adverse reactions in patients treated with JANUVIA was as follows: abdominal pain (JANUVIA 100 mg, 2.3%; placebo, 2.1%), nausea (1.4%, 0.6%), and diarrhea (3.0%, 2.3%).

In an additional, 24-week, placebo-controlled factorial study of initial therapy with sitagliptin in combination with metformin, the adverse reactions reported (regardless of investigator assessment of causality) in  $\geq 5\%$  of patients are shown in Table 2.

**Table 2:**  
**Initial Therapy with Combination of Sitagliptin and Metformin:**  
**Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in ≥5% of Patients**  
**Receiving Combination Therapy (and Greater than in Patients Receiving Metformin alone, Sitagliptin**  
**alone, and Placebo)\***

	Number of Patients (%)			
	Placebo	Sitagliptin (JANUVIA) 100 mg QD	Metformin 500 or 1000 mg bid <sup>†</sup>	Sitagliptin 50 mg bid + Metformin 500 or 1000 mg bid <sup>†</sup>
	N = 176	N = 179	N = 364 <sup>†</sup>	N = 372 <sup>†</sup>
Upper Respiratory 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.

<sup>†</sup> Data pooled for the patients given the lower and higher doses of metformin.

In a 24-week study of initial therapy with JANUVIA in combination with pioglitazone, there were no adverse reactions reported (regardless of investigator assessment of causality) in ≥5% of patients and more commonly than in patients given pioglitazone alone.

No clinically meaningful changes in vital signs or in ECG (including in QTc interval) were observed in patients treated with JANUVIA.

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 (5.1).*]

**Hypoglycemia**

In all (N=9) studies, adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia. A concurrent blood glucose measurement was not required although most (74%) reports of hypoglycemia were accompanied by a blood glucose measurement ≤70 mg/dL. When JANUVIA was coadministered with a sulfonyleurea or with insulin, the percentage of patients with at least one adverse reaction of hypoglycemia was higher than in the corresponding placebo group (Table 3).

**Table 3:**  
**Incidence and Rate of Hypoglycemia\* in Placebo-Controlled Clinical Studies when JANUVIA was used**  
**as Add-On Therapy to Glimepiride (with or without Metformin) or Insulin (with or without Metformin),**  
**Regardless of Investigator Assessment of Causality**

Add-On to Glimepiride (+/- Metformin) (24 weeks)	JANUVIA 100 mg + Glimepiride (+/- Metformin)	Placebo + Glimepiride (+/- Metformin)
	N = 222	N = 219
Overall (%)	27 (12.2)	4 (1.8)
Rate (episodes/patient-year) <sup>†</sup>	0.59	0.24
Severe (%) <sup>‡</sup>	0 (0.0)	0 (0.0)
Add-On to Insulin (+/- Metformin) (24 weeks)	JANUVIA 100 mg + Insulin (+/- Metformin)	Placebo + Insulin (+/- Metformin)
	N = 322	N = 319
Overall (%)	50 (15.5)	25 (7.8)
Rate (episodes/patient-year) <sup>†</sup>	1.06	0.51
Severe (%) <sup>‡</sup>	2 (0.6)	1 (0.3)

\* 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.

In a pooled analysis of the two monotherapy studies, the add-on to metformin study, and the add-on to pioglitazone study, the overall incidence of adverse reactions of hypoglycemia was 1.2% in patients treated with JANUVIA 100 mg and 0.9% in patients treated with placebo.

In the study of JANUVIA as add-on combination therapy with metformin and rosiglitazone, the overall incidence of hypoglycemia was 2.2% in patients given add-on JANUVIA 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 JANUVIA and 1.0% in patients given add-on placebo.

In the 24-week, placebo-controlled factorial study of initial therapy with JANUVIA in combination with metformin, the incidence of hypoglycemia was 0.6% in patients given placebo, 0.6% in patients given JANUVIA alone, 0.8% in patients given metformin alone, and 1.6% in patients given JANUVIA in combination with metformin.

In the study of JANUVIA as initial therapy with pioglitazone, one patient taking JANUVIA experienced a severe episode of hypoglycemia. There were no severe hypoglycemia episodes reported in other studies except in the study involving coadministration with insulin.

#### *Laboratory Tests*

Across clinical studies, the incidence of laboratory adverse reactions was similar in patients treated with JANUVIA 100 mg compared to patients treated with placebo. A small increase in white blood cell count (WBC) was observed due to an increase in neutrophils. This increase in WBC (of approximately 200 cells/microL vs placebo, in four pooled placebo-controlled clinical studies, with a mean baseline WBC count of approximately 6600 cells/microL) is not considered to be clinically relevant. In a 12-week study of 91 patients with chronic renal insufficiency, 37 patients with moderate renal insufficiency were randomized to JANUVIA 50 mg daily, while 14 patients with the same magnitude of renal impairment were randomized to placebo. Mean (SE) increases in serum creatinine were observed in patients treated with JANUVIA [0.12 mg/dL (0.04)] and in patients treated with placebo [0.07 mg/dL (0.07)]. The clinical significance of this added increase in serum creatinine relative to placebo is not known.

### **6.2 Postmarketing Experience**

Additional adverse reactions have been identified during postapproval use of JANUVIA as monotherapy and/or in combination with other antihyperglycemic agents. 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* (5.4)]; hepatic enzyme elevations; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis [see *Indications and Usage* (1.2); *Warnings and Precautions* (5.1)]; worsening renal function, including acute renal failure (sometimes requiring dialysis) [see *Warnings and Precautions* (5.2)]; severe and disabling arthralgia [see *Warnings and Precautions* (5.5)]; constipation; vomiting; headache; myalgia; pain in extremity; back pain; pruritus.

## **7 DRUG INTERACTIONS**

### **7.1 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 JANUVIA is recommended.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### *Pregnancy Category B:*

Reproduction studies have been performed in rats and rabbits. Doses of sitagliptin up to 125 mg/kg (approximately 12 times the human exposure at the maximum recommended human dose) did not impair fertility or harm the fetus. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., maintains a registry to monitor the pregnancy outcomes of women exposed to JANUVIA while pregnant. Health care providers are encouraged to report any prenatal exposure to JANUVIA by calling the Pregnancy Registry at 1-800-986-8999.

Sitagliptin administered to pregnant female rats and rabbits from gestation day 6 to 20 (organogenesis) was not teratogenic at oral doses up to 250 mg/kg (rats) and 125 mg/kg (rabbits), or

approximately 30- and 20-times human exposure at the maximum recommended human dose (MRHD) of 100 mg/day based on AUC comparisons. Higher doses increased the incidence of rib malformations in offspring at 1000 mg/kg, or approximately 100 times human exposure at the MRHD.

Sitagliptin administered to female rats from gestation day 6 to lactation day 21 decreased body weight in male and female offspring at 1000 mg/kg. No functional or behavioral toxicity was observed in offspring of rats.

Placental transfer of sitagliptin administered to pregnant rats was approximately 45% at 2 hours and 80% at 24 hours postdose. Placental transfer of sitagliptin administered to pregnant rabbits was approximately 66% at 2 hours and 30% at 24 hours.

### **8.3 Nursing Mothers**

Sitagliptin is secreted in the milk of lactating rats at a milk to plasma ratio of 4:1. It is not known whether sitagliptin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when JANUVIA is administered to a nursing woman.

### **8.4 Pediatric Use**

Safety and effectiveness of JANUVIA in pediatric patients under 18 years of age have not been established.

### **8.5 Geriatric Use**

Of the total number of subjects (N=3884) in pre-approval clinical safety and efficacy studies of JANUVIA, 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.

This drug is known to be substantially excreted by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly, and it may be useful to assess renal function in these patients prior to initiating dosing and periodically thereafter [see *Dosage and Administration (2.2); Clinical Pharmacology (12.3)*].

## **10 OVERDOSAGE**

During controlled clinical trials in healthy subjects, single doses of up to 800 mg JANUVIA were administered. Maximal mean increases in QTc of 8.0 msec were observed in one study at a dose of 800 mg JANUVIA, 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 JANUVIA with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for 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 dictated by the patient's clinical status.

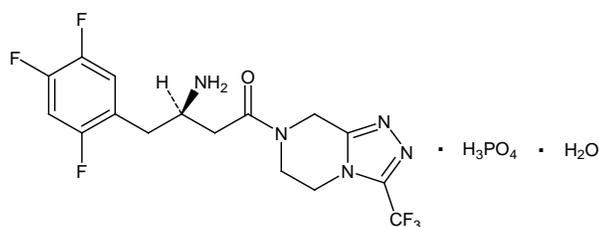
Sitagliptin is modestly dialyzable. In clinical studies, approximately 13.5% of the dose was removed over a 3- to 4-hour hemodialysis session. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialyzable by peritoneal dialysis.

## **11 DESCRIPTION**

JANUVIA Tablets contain sitagliptin phosphate, an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme.

Sitagliptin phosphate monohydrate is described chemically as 7-[(3*R*)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyrazine phosphate (1:1) monohydrate.

The empirical formula is C<sub>16</sub>H<sub>15</sub>F<sub>6</sub>N<sub>5</sub>O•H<sub>3</sub>PO<sub>4</sub>•H<sub>2</sub>O and the molecular weight is 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.

Each film-coated tablet of JANUVIA contains 32.13, 64.25, or 128.5 mg of sitagliptin phosphate monohydrate, which is equivalent to 25, 50, or 100 mg, respectively, of free base and the following inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, and sodium stearyl fumarate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, red iron oxide, and yellow iron oxide.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Sitagliptin is a DPP-4 inhibitor, which is believed to exert its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased by JANUVIA, 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, JANUVIA 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.

### 12.2 Pharmacodynamics

#### General

In patients with type 2 diabetes, administration of JANUVIA 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 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 how these findings relate to changes in glycemic control in patients with type 2 diabetes.

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

#### Cardiac Electrophysiology

In a randomized, placebo-controlled crossover study, 79 healthy subjects were administered a single oral dose of JANUVIA 100 mg, JANUVIA 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 was observed at 3 hours postdose and 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 administered JANUVIA 100 mg (N=81) or JANUVIA 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

The pharmacokinetics of sitagliptin has been extensively characterized in healthy subjects and patients with type 2 diabetes. After oral administration of a 100 mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median  $T_{max}$ ) occurring 1 to 4 hours postdose. Plasma AUC of sitagliptin increased in a dose-proportional manner. Following a single oral 100 mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8.52  $\mu\text{M}\cdot\text{hr}$ ,  $C_{max}$  was 950 nM, and apparent terminal half-life ( $t_{1/2}$ ) was 12.4 hours. Plasma AUC of sitagliptin 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.

#### *Absorption*

The absolute bioavailability of sitagliptin is approximately 87%. Because coadministration of a high-fat meal with JANUVIA had no effect on the pharmacokinetics, JANUVIA may be administered with or without food.

#### *Distribution*

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%).

#### *Metabolism*

Approximately 79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination.

Following a [ $^{14}\text{C}$ ]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.

#### *Excretion*

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

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, which may also be involved in mediating the renal elimination of sitagliptin. However, cyclosporine, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin.

#### *Special Populations*

##### *Renal Insufficiency*

A single-dose, open-label study was conducted to evaluate the pharmacokinetics of JANUVIA (50 mg dose) in patients with varying degrees of chronic renal insufficiency compared to normal healthy control subjects. The study included patients with renal insufficiency classified on the basis of creatinine clearance as mild (50 to <80 mL/min), moderate (30 to <50 mL/min), and severe (<30 mL/min), as well as patients with ESRD on hemodialysis. In addition, the effects of renal insufficiency on sitagliptin pharmacokinetics in patients with type 2 diabetes and mild or moderate renal insufficiency were assessed using population pharmacokinetic analyses. Creatinine clearance was measured by 24-hour urinary creatinine clearance measurements or estimated from serum creatinine based on the Cockcroft-Gault formula:

$$\text{CrCl} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)} \{ \times 0.85 \text{ for female patients} \}}{[72 \times \text{serum creatinine (mg/dL)}]}$$

Compared to normal healthy control subjects, an approximate 1.1- to 1.6-fold increase in plasma AUC of sitagliptin was observed in patients with mild renal insufficiency. Because increases of this magnitude are not clinically relevant, dosage adjustment in patients with mild renal insufficiency is not necessary. Plasma AUC levels of sitagliptin were increased approximately 2-fold and 4-fold in patients with moderate renal insufficiency and in patients with severe renal insufficiency, including patients with ESRD on hemodialysis, respectively. Sitagliptin was modestly removed by hemodialysis (13.5% over a 3- to 4-hour hemodialysis session starting 4 hours postdose). To achieve plasma concentrations of sitagliptin similar to those in patients with normal renal function, lower dosages are recommended in patients with moderate and severe renal insufficiency, as well as in ESRD patients requiring dialysis. [See *Dosage and Administration (2.2).*]

#### *Hepatic Insufficiency*

In patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), mean AUC and  $C_{max}$  of sitagliptin increased approximately 21% and 13%, respectively, compared to healthy matched controls following administration of a single 100 mg dose of JANUVIA. These differences are not considered to be clinically meaningful. No dosage adjustment for JANUVIA is necessary for patients with mild or moderate hepatic insufficiency.

There is no clinical experience in patients with severe hepatic insufficiency (Child-Pugh score >9).

#### *Body Mass Index (BMI)*

No dosage adjustment is necessary based on BMI. Body mass index had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

#### *Gender*

No dosage adjustment is necessary based on gender. Gender had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

#### *Geriatric*

No dosage adjustment is required based solely on age. 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.

#### *Pediatric*

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

#### *Race*

No dosage adjustment is necessary based on race. Race had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of available pharmacokinetic data, including subjects of white, Hispanic, black, Asian, and other racial groups.

#### *Drug Interactions*

##### *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-glycoprotein substrate, but does not inhibit p-glycoprotein 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, as described below, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, warfarin, or oral contraceptives, providing *in vivo* evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cationic transporter (OCT).

*Digoxin:* Sitagliptin had a minimal effect on the pharmacokinetics of digoxin. Following administration of 0.25 mg digoxin concomitantly with 100 mg of JANUVIA daily for 10 days, the plasma AUC of digoxin was increased by 11%, and the plasma  $C_{max}$  by 18%.

*Metformin:* Coadministration of multiple twice-daily doses of sitagliptin with metformin, an OCT substrate, did not meaningfully alter the pharmacokinetics of metformin in patients with type 2 diabetes. Therefore, sitagliptin is not an inhibitor of OCT-mediated transport.

*Sulfonylureas:* Single-dose pharmacokinetics of glyburide, a CYP2C9 substrate, was not meaningfully altered in subjects receiving multiple doses of sitagliptin. Clinically meaningful interactions would not be expected with other sulfonylureas (e.g., glipizide, tolbutamide, and glimepiride) which, like glyburide, are primarily eliminated by CYP2C9.

*Simvastatin:* Single-dose pharmacokinetics of simvastatin, a CYP3A4 substrate, was not meaningfully altered in subjects receiving multiple daily doses of sitagliptin. Therefore, sitagliptin is not an inhibitor of CYP3A4-mediated metabolism.

*Thiazolidinediones:* Single-dose pharmacokinetics of rosiglitazone was not meaningfully altered in subjects receiving multiple daily doses of sitagliptin, indicating that JANUVIA is not an inhibitor of CYP2C8-mediated metabolism.

*Warfarin:* Multiple daily doses of sitagliptin did not meaningfully alter the pharmacokinetics, as assessed by measurement of S(-) or R(+) warfarin enantiomers, or pharmacodynamics (as assessed by measurement of prothrombin INR) of a single dose of warfarin. Because S(-) warfarin is primarily metabolized by CYP2C9, these data also support the conclusion that sitagliptin is not a CYP2C9 inhibitor.

*Oral Contraceptives:* Coadministration with sitagliptin did not meaningfully alter the steady-state pharmacokinetics of norethindrone or ethinyl estradiol.

#### Effects of Other Drugs on Sitagliptin

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

*Metformin:* Coadministration of multiple twice-daily doses of metformin with sitagliptin did not meaningfully alter the pharmacokinetics of sitagliptin in patients with type 2 diabetes.

*Cyclosporine:* A study was conducted to assess the effect of cyclosporine, a potent inhibitor of p-glycoprotein, on the pharmacokinetics of sitagliptin. Coadministration of a single 100 mg oral dose of JANUVIA and a single 600 mg oral dose of cyclosporine increased the AUC and  $C_{max}$  of sitagliptin by approximately 29% and 68%, respectively. These modest changes in sitagliptin pharmacokinetics were not considered to be clinically meaningful. The renal clearance of sitagliptin was also not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors.

## **13 NONCLINICAL TOXICOLOGY**

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

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).

## **14 CLINICAL STUDIES**

There were approximately 5200 patients with type 2 diabetes randomized in nine double-blind, placebo-controlled clinical safety and efficacy studies conducted to evaluate the effects of sitagliptin on

glycemic control. In a pooled analysis of seven of these studies, the ethnic/racial distribution was approximately 59% white, 20% Hispanic, 10% Asian, 6% black, and 6% other groups. Patients had an overall mean age of approximately 55 years (range 18 to 87 years). In addition, an active (glipizide)-controlled study of 52-weeks duration was conducted in 1172 patients with type 2 diabetes who had inadequate glycemic control on metformin.

In patients with type 2 diabetes, treatment with JANUVIA produced clinically significant improvements in hemoglobin A1C, fasting plasma glucose (FPG) and 2-hour post-prandial glucose (PPG) compared to placebo.

#### **14.1 Monotherapy**

A total of 1262 patients with type 2 diabetes participated in two double-blind, placebo-controlled studies, one of 18-week and another of 24-week duration, to evaluate the efficacy and safety of JANUVIA monotherapy. In both monotherapy studies, patients currently on an antihyperglycemic agent discontinued the agent, and underwent a diet, exercise, and drug washout period of about 7 weeks. Patients with inadequate glycemic control (A1C 7% to 10%) after the washout period were randomized after completing a 2-week single-blind placebo run-in period; patients not currently on antihyperglycemic agents (off therapy for at least 8 weeks) with inadequate glycemic control (A1C 7% to 10%) were randomized after completing the 2-week single-blind placebo run-in period. In the 18-week study, 521 patients were randomized to placebo, JANUVIA 100 mg, or JANUVIA 200 mg, and in the 24-week study 741 patients were randomized to placebo, JANUVIA 100 mg, or JANUVIA 200 mg. Patients who failed to meet specific glycemic goals during the studies were treated with metformin rescue, added on to placebo or JANUVIA.

Treatment with JANUVIA at 100 mg daily provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo (Table 4). In the 18-week study, 9% of patients receiving JANUVIA 100 mg and 17% who received placebo required rescue therapy. In the 24-week study, 9% of patients receiving JANUVIA 100 mg and 21% of patients receiving placebo required rescue therapy. The improvement in A1C compared to placebo was not affected by gender, age, race, prior antihyperglycemic therapy, or baseline BMI. As is typical for trials of agents to treat type 2 diabetes, the mean reduction in A1C with JANUVIA appears to be related to the degree of A1C elevation at baseline. In these 18- and 24-week studies, among patients who were not on an antihyperglycemic agent at study entry, the reductions from baseline in A1C were -0.7% and -0.8%, respectively, for those given JANUVIA, and -0.1% and -0.2%, respectively, for those given placebo. Overall, the 200 mg daily dose did not provide greater glycemic efficacy than the 100 mg daily dose. The effect of JANUVIA on lipid endpoints was similar to placebo. Body weight did not increase from baseline with JANUVIA therapy in either study, compared to a small reduction in patients given placebo.

**Table 4:**  
**Glycemic Parameters in 18- and 24-Week Placebo-Controlled Studies of JANUVIA in Patients with Type 2 Diabetes\***

	18-Week Study		24-Week Study	
	JANUVIA 100 mg	Placebo	JANUVIA 100 mg	Placebo
<b>A1C (%)</b>	<b>N = 193</b>	<b>N = 103</b>	<b>N = 229</b>	<b>N = 244</b>
Baseline (mean)	8.0	8.1	8.0	8.0
Change from baseline (adjusted mean <sup>†</sup> )	-0.5	0.1	-0.6	0.2
Difference from placebo (adjusted mean <sup>†</sup> ) (95% CI)	-0.6 <sup>‡</sup> (-0.8, -0.4)		-0.8 <sup>‡</sup> (-1.0, -0.6)	
Patients (%) achieving A1C <7%	69 (36%)	16 (16%)	93 (41%)	41 (17%)
<b>FPG (mg/dL)</b>	<b>N = 201</b>	<b>N = 107</b>	<b>N = 234</b>	<b>N = 247</b>
Baseline (mean)	180	184	170	176
Change from baseline (adjusted mean <sup>†</sup> )	-13	7	-12	5
Difference from placebo (adjusted mean <sup>†</sup> ) (95% CI)	-20 <sup>‡</sup> (-31, -9)		-17 <sup>‡</sup> (-24, -10)	
<b>2-hour PPG (mg/dL)</b>	§	§	<b>N = 201</b>	<b>N = 204</b>
Baseline (mean)			257	271
Change from baseline (adjusted mean <sup>†</sup> )			-49	-2
Difference from placebo (adjusted mean <sup>†</sup> ) (95% CI)			-47 <sup>‡</sup> (-59, -34)	

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

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

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

<sup>§</sup> Data not available.

#### *Additional Monotherapy Study*

A multinational, randomized, double-blind, placebo-controlled study was also conducted to assess the safety and tolerability of JANUVIA in 91 patients with type 2 diabetes and chronic renal insufficiency (creatinine clearance <50 mL/min). Patients with moderate renal insufficiency received 50 mg daily of JANUVIA and those with severe renal insufficiency or with ESRD on hemodialysis or peritoneal dialysis received 25 mg daily. In this study, the safety and tolerability of JANUVIA were generally similar to placebo. A small increase in serum creatinine was reported in patients with moderate renal insufficiency treated with JANUVIA relative to those on placebo. In addition, the reductions in A1C and FPG with JANUVIA compared to placebo were generally similar to those observed in other monotherapy studies. [See *Clinical Pharmacology* (12.3).]

#### **14.2 Combination Therapy**

##### *Add-on Combination Therapy with Metformin*

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 JANUVIA in combination with metformin. Patients already on metformin (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 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 (at a dose of at least 1500 mg per day) in monotherapy. Patients with inadequate glycemic control (A1C 7% to 10%) were randomized to the addition of either 100 mg of JANUVIA 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, JANUVIA provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo with metformin (Table 5). Rescue glycemic therapy was used in 5% of patients treated with JANUVIA 100 mg and 14% of patients treated with placebo. A similar decrease in body weight was observed for both treatment groups.

**Table 5:  
Glycemic Parameters at Final Visit (24-Week Study)  
for JANUVIA in Add-on Combination Therapy with Metformin\***

	<b>JANUVIA 100 mg + Metformin</b>	<b>Placebo + Metformin</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 (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 (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 (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.

#### *Initial Combination Therapy with Metformin*

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 as initial therapy in combination with metformin. Patients on an antihyperglycemic agent (N=541) discontinued the agent, and 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 initial therapy with placebo, 100 mg of JANUVIA once daily, 500 mg or 1000 mg of metformin twice daily, or 50 mg of sitagliptin twice daily in combination with 500 mg or 1000 mg of metformin twice daily. Patients who failed to meet specific glycemic goals during the study were treated with glyburide (glibenclamide) rescue.

Initial therapy with the combination of JANUVIA and metformin provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo, to metformin alone, and to JANUVIA alone (Table 6, Figure 1). Mean reductions from baseline in A1C were generally greater for patients with higher baseline A1C values. For patients not on an antihyperglycemic agent at study entry, mean reductions from baseline in A1C were: JANUVIA 100 mg once daily, -1.1%; metformin 500 mg bid, -1.1%; metformin 1000 mg bid, -1.2%; sitagliptin 50 mg bid with metformin 500 mg bid, -1.6%; sitagliptin 50 mg bid with metformin 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 was similar to that in the groups given metformin alone or placebo.

**Table 6:  
Glycemic Parameters at Final Visit (24-Week Study)  
for Sitagliptin and Metformin, Alone and in Combination as Initial Therapy\***

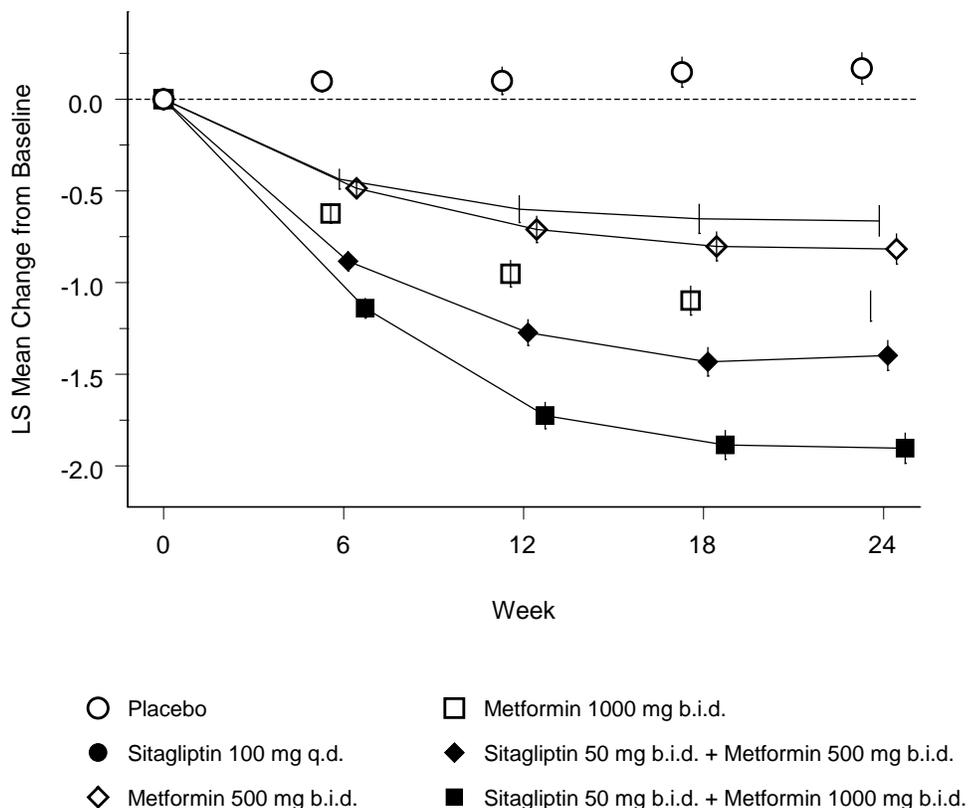
	Placebo	Sitagliptin (JANUVIA) 100 mg QD	Metformin 500 mg bid	Metformin 1000 mg bid	Sitagliptin 50 mg bid + Metformin 500 mg bid	Sitagliptin 50 mg bid + Metformin 1000 mg bid
<b>A1C (%)</b>	<b>N = 165</b>	<b>N = 175</b>	<b>N = 178</b>	<b>N = 177</b>	<b>N = 183</b>	<b>N = 178</b>
Baseline (mean)	8.7	8.9	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, Alone and in Combination as Initial Therapy in Patients with Type 2 Diabetes\***



\*All Patients Treated Population: least squares means adjusted for prior antihyperglycemic therapy and baseline value.

Initial combination therapy or maintenance of combination therapy may not be appropriate for all patients. These management options are left to the discretion of the health care provider.

*Active-Controlled Study vs Glipizide in Combination with Metformin*

The efficacy of JANUVIA 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 monotherapy (dose of  $\geq 1500$  mg per day) which included washout of medications other than metformin, 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 JANUVIA 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.

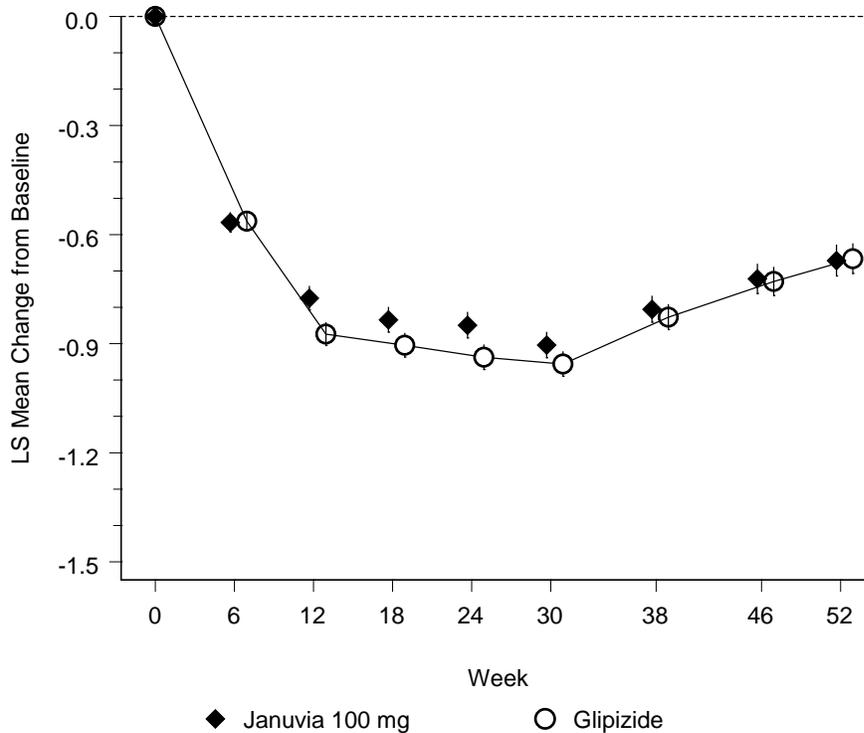
After 52 weeks, JANUVIA and glipizide had similar mean reductions from baseline in A1C in the intent-to-treat analysis (Table 7). These results were consistent with the per protocol analysis (Figure 2). A conclusion in favor of the non-inferiority of JANUVIA to glipizide may be limited to patients with baseline A1C comparable to those included in the study (over 70% of patients had baseline A1C <8% and over 90% had A1C <9%).

**Table 7:  
Glycemic Parameters in a 52-Week Study Comparing  
JANUVIA to Glipizide as Add-On Therapy in Patients Inadequately  
Controlled on Metformin  
(Intent-to-Treat Population)\***

	<b>JANUVIA 100 mg</b>	<b>Glipizide</b>
<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 JANUVIA to Glipizide as Add-On Therapy in  
Patients Inadequately Controlled on Metformin  
(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 JANUVIA group (4.9%) was significantly ( $p < 0.001$ ) lower than that in the glipizide group (32.0%). Patients treated with JANUVIA 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).

### Add-on Combination Therapy with Pioglitazone

A total of 353 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of JANUVIA in combination with pioglitazone. Patients on any oral antihyperglycemic agent in monotherapy (N=212) or on a PPAR $\gamma$  agent in combination therapy (N=106) or not on an antihyperglycemic agent (off therapy for at least 8 weeks, N=34) were switched to monotherapy with pioglitazone (at a dose of 30-45 mg per day), and completed a run-in period of approximately 12 weeks in duration. After the run-in period on pioglitazone monotherapy, patients with inadequate glycemic control (A1C 7% to 10%) were randomized to the addition of either 100 mg of JANUVIA or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with metformin rescue. Glycemic endpoints measured were A1C and fasting glucose.

In combination with pioglitazone, JANUVIA provided significant improvements in A1C and FPG compared to placebo with pioglitazone (Table 8). Rescue therapy was used in 7% of patients treated with JANUVIA 100 mg and 14% of patients treated with placebo. There was no significant difference between JANUVIA and placebo in body weight change.

**Table 8:**  
**Glycemic Parameters at Final Visit (24-Week Study)**  
**for JANUVIA in Add-on Combination Therapy with Pioglitazone\***

	<b>JANUVIA 100 mg + Pioglitazone</b>	<b>Placebo + Pioglitazone</b>
<b>A1C (%)</b>	<b>N = 163</b>	<b>N = 174</b>
Baseline (mean)	8.1	8.0
Change from baseline (adjusted mean <sup>†</sup> )	-0.9	-0.2
Difference from placebo + pioglitazone (adjusted mean <sup>†</sup> ) (95% CI)	-0.7 <sup>‡</sup> (-0.9, -0.5)	
Patients (%) achieving A1C <7%	74 (45%)	40 (23%)
<b>FPG (mg/dL)</b>	<b>N = 163</b>	<b>N = 174</b>
Baseline (mean)	168	166
Change from baseline (adjusted mean <sup>†</sup> )	-17	1
Difference from placebo + pioglitazone (adjusted mean <sup>†</sup> ) (95% CI)	-18 <sup>‡</sup> (-24, -11)	

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

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

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

### Initial Combination Therapy with Pioglitazone

A total of 520 patients with type 2 diabetes and inadequate glycemic control on diet and exercise participated in a 24-week, randomized, double-blind study designed to assess the efficacy of JANUVIA as initial therapy in combination with pioglitazone. Patients not on antihyperglycemic agents at study entry (<4 weeks cumulative therapy over the past 2 years, and with no treatment over the prior 4 months) with inadequate glycemic control (A1C 8% to 12%) immediately entered the 2-week single-blind placebo run-in period and then were randomized. Approximately equal numbers of patients were randomized to receive initial therapy with 100 mg of JANUVIA in combination with 30 mg of pioglitazone once daily or 30 mg of pioglitazone once daily as monotherapy. There was no glycemic rescue therapy in this study.

Initial therapy with the combination of JANUVIA and pioglitazone provided significant improvements in A1C, FPG, and 2-hour PPG compared to pioglitazone monotherapy (Table 9). The improvement in A1C was generally consistent across subgroups defined by gender, age, race, baseline BMI, baseline A1C, or duration of disease. In this study, patients treated with JANUVIA in combination with pioglitazone had a mean increase in body weight of 1.1 kg compared to pioglitazone alone (3.0 kg vs. 1.9 kg). Lipid effects were generally neutral.

**Table 9:  
Glycemic Parameters at Final Visit (24-Week Study)  
for JANUVIA in Combination with Pioglitazone as Initial Therapy\***

	<b>JANUVIA 100 mg + Pioglitazone</b>	<b>Pioglitazone</b>
<b>A1C (%)</b>	<b>N = 251</b>	<b>N = 246</b>
Baseline (mean)	9.5	9.4
Change from baseline (adjusted mean <sup>†</sup> )	-2.4	-1.5
Difference from pioglitazone (adjusted mean <sup>†</sup> ) (95% CI)	-0.9 <sup>‡</sup> (-1.1, -0.7)	
Patients (%) achieving A1C <7%	151 (60%)	68 (28%)
<b>FPG (mg/dL)</b>	<b>N = 256</b>	<b>N = 253</b>
Baseline (mean)	203	201
Change from baseline (adjusted mean <sup>†</sup> )	-63	-40
Difference from pioglitazone (adjusted mean <sup>†</sup> ) (95% CI)	-23 <sup>‡</sup> (-30, -15)	
<b>2-hour PPG (mg/dL)</b>	<b>N = 216</b>	<b>N = 211</b>
Baseline (mean)	283	284
Change from baseline (adjusted mean <sup>†</sup> )	-114	-69
Difference from pioglitazone (adjusted mean <sup>†</sup> ) (95% CI)	-45 <sup>‡</sup> (-57, -32)	

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

<sup>†</sup> Least squares means adjusted for baseline value.

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

#### *Add-on Combination Therapy with Metformin 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 JANUVIA in combination with metformin and rosiglitazone. Patients on dual therapy with metformin ≥1500 mg/day and rosiglitazone ≥4 mg/day or with metformin ≥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 ≥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 JANUVIA or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the study were treated with glipizide (or other sulfonylurea) rescue. The primary time point for evaluation of glycemic parameters was Week 18.

In combination with metformin and rosiglitazone, JANUVIA provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo with metformin and rosiglitazone (Table 10) at Week 18. At Week 54, mean reduction in A1C was -1.0% for patients treated with JANUVIA 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 JANUVIA 100 mg and 40% of patients treated with placebo. There was no significant difference between JANUVIA and placebo in body weight change.

**Table 10:  
Glycemic Parameters at Week 18  
for JANUVIA in Add-on Combination Therapy with Metformin and Rosiglitazone\***

	<b>JANUVIA 100 mg + Metformin + Rosiglitazone</b>	<b>Placebo + Metformin + Rosiglitazone</b>
<b>A1C (%)</b>	<b>N = 176</b>	<b>N = 93</b>
Baseline (mean)	8.8	8.7
Change from baseline (adjusted mean <sup>†</sup> )	-1.0	-0.4
Difference from placebo + rosiglitazone + metformin (adjusted mean <sup>†</sup> ) (95% CI)	-0.7 <sup>‡</sup> (-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 <sup>†</sup> )	-30	-11
Difference from placebo + rosiglitazone + metformin (adjusted mean <sup>†</sup> ) (95% CI)	-18 <sup>‡</sup> (-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 <sup>†</sup> )	-59	-21
Difference from placebo + rosiglitazone + metformin (adjusted mean <sup>†</sup> ) (95% CI)	-39 <sup>‡</sup> (-51, -26)	

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

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

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

**Add-on Combination Therapy with Glimepiride, with or without Metformin**

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 JANUVIA in combination with glimepiride, with or without metformin. Patients entered a run-in treatment period on glimepiride (≥4 mg per day) alone or glimepiride in combination with metformin (≥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 JANUVIA or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with pioglitazone rescue.

In combination with glimepiride, with or without metformin, JANUVIA provided significant improvements in A1C and FPG compared to placebo (Table 11). In the entire study population (patients on JANUVIA in combination with glimepiride and patients on JANUVIA in combination with glimepiride and metformin), a mean reduction from baseline relative to placebo in A1C of -0.7% and in FPG of -20 mg/dL was seen. Rescue therapy was used in 12% of patients treated with JANUVIA 100 mg and 27% of patients treated with placebo. In this study, patients treated with JANUVIA had a mean increase in body weight of 1.1 kg vs. placebo (+0.8 kg vs. -0.4 kg). In addition, there was an increased rate of hypoglycemia. [See *Warnings and Precautions* (5.3); *Adverse Reactions* (6.1).]

**Table 11:**  
**Glycemic Parameters at Final Visit (24-Week Study)**  
**for JANUVIA as Add-On Combination Therapy with Glimepiride, with or without Metformin\***

	<b>JANUVIA 100 mg + Glimepiride</b>	<b>Placebo + Glimepiride</b>	<b>JANUVIA 100 mg + Glimepiride + Metformin</b>	<b>Placebo + Glimepiride + Metformin</b>
<b>A1C (%)</b>	<b>N = 102</b>	<b>N = 103</b>	<b>N = 115</b>	<b>N = 105</b>
Baseline (mean)	8.4	8.5	8.3	8.3
Change from baseline (adjusted mean <sup>†</sup> )	-0.3	0.3	-0.6	0.3
Difference from placebo (adjusted mean <sup>†</sup> ) (95% CI)	-0.6 <sup>‡</sup> (-0.8, -0.3)		-0.9 <sup>‡</sup> (-1.1, -0.7)	
Patients (%) achieving A1C <7%	11 (11%)	9 (9%)	26 (23%)	1 (1%)
<b>FPG (mg/dL)</b>	<b>N = 104</b>	<b>N = 104</b>	<b>N = 115</b>	<b>N = 109</b>
Baseline (mean)	183	185	179	179
Change from baseline (adjusted mean <sup>†</sup> )	-1	18	-8	13
Difference from placebo (adjusted mean <sup>†</sup> ) (95% CI)	-19 <sup>§</sup> (-32, -7)		-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.

<sup>§</sup> p<0.01 compared to placebo.

***Add-on Combination Therapy with Insulin (with or without Metformin)***

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 JANUVIA as add-on to insulin therapy (with or without metformin). The racial distribution in this study was approximately 70% white, 18% Asian, 7% black, and 5% other groups. Approximately 14% of the patients in this study were Hispanic. Patients entered a 2-week, single-blind run-in treatment period on pre-mixed, long-acting, or intermediate-acting insulin, with or without metformin (≥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 JANUVIA or placebo, 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.

The median daily insulin dose at baseline was 42 units in the patients treated with JANUVIA and 45 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. In combination with insulin (with or without metformin), JANUVIA provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo (Table 12). Both treatment groups had an adjusted mean increase in body weight of 0.1 kg from baseline to Week 24. There was an increased rate of hypoglycemia in patients treated with JANUVIA. [See *Warnings and Precautions* (5.3); *Adverse Reactions* (6.1).]

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

	<b>JANUVIA 100 mg + Insulin (+/- Metformin)</b>	<b>Placebo + Insulin (+/- Metformin)</b>
<b>A1C (%)</b>	<b>N = 305</b>	<b>N = 312</b>
Baseline (mean)	8.7	8.6
Change from baseline (adjusted mean <sup>†</sup> )	-0.6	-0.1
Difference from placebo (adjusted mean <sup>†,‡</sup> ) (95% CI)	-0.6 <sup>§</sup> (-0.7, -0.4)	
Patients (%) achieving A1C <7%	39 (12.8%)	16 (5.1%)
<b>FPG (mg/dL)</b>	<b>N = 310</b>	<b>N = 313</b>
Baseline (mean)	176	179
Change from baseline (adjusted mean <sup>†</sup> )	-18	-4
Difference from placebo (adjusted mean <sup>†</sup> ) (95% CI)	-15 <sup>§</sup> (-23, -7)	
<b>2-hour PPG (mg/dL)</b>	<b>N = 240</b>	<b>N = 257</b>
Baseline (mean)	291	292
Change from baseline (adjusted mean <sup>†</sup> )	-31	5
Difference from placebo (adjusted mean <sup>†</sup> ) (95% CI)	-36 <sup>§</sup> (-47, -25)	

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

<sup>†</sup> Least squares means adjusted for metformin use at the screening visit (yes/no), 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 stratum interaction was not significant (p>0.10) for metformin stratum and for insulin stratum.

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

## 16 HOW SUPPLIED/STORAGE AND HANDLING

No. 6737 — Tablets JANUVIA, 25 mg, are pink, round, film-coated tablets with “221” on one side. They are supplied as follows:

- NDC 0006-0221-31 unit-of-use bottles of 30
- NDC 0006-0221-54 unit-of-use bottles of 90
- NDC 0006-0221-28 unit dose blister packages of 100.

No. 6738 — Tablets JANUVIA, 50 mg, are light beige, round, film-coated tablets with “112” on one side. They are supplied as follows:

- NDC 0006-0112-31 unit-of-use bottles of 30
- NDC 0006-0112-54 unit-of-use bottles of 90
- NDC 0006-0112-28 unit dose blister packages of 100.

No. 6739 — Tablets JANUVIA, 100 mg, are beige, round, film-coated tablets with “277” on one side. They are supplied as follows:

- NDC 0006-0277-31 unit-of-use bottles of 30
- NDC 0006-0277-54 unit-of-use bottles of 90
- NDC 0006-0277-02 unit-of-use blister calendar package of 30
- NDC 0006-0277-33 unit-of-use blister calendar package of 30
- NDC 0006-0277-28 unit dose blister packages of 100
- NDC 0006-0277-82 bottles of 1000.

### Storage

Store at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.]

## 17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Medication Guide).

### 17.1 Instructions

Patients should be informed of the potential risks and benefits of JANUVIA and of alternative modes of therapy. Patients 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.

Patients should be informed that acute pancreatitis has been reported during postmarketing use of JANUVIA. 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 JANUVIA and contact their physician if persistent severe abdominal pain occurs [see *Warnings and Precautions (5.1)*].

Patients should be informed that the incidence of hypoglycemia is increased when JANUVIA is added to a sulfonylurea or insulin and that a lower dose of the sulfonylurea 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 JANUVIA. 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 JANUVIA 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 (5.5)*].

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

### 17.2 Laboratory Tests

Patients should be informed that 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. Patients should be informed of the potential need to adjust dose based on changes in renal function tests over time.

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uspi-mk0431-t-1508r016

**Medication Guide**  
**JANUVIA® (jah-NEW-vee-ah)**  
**(sitagliptin)**  
**Tablets**

Read this Medication Guide carefully before you start taking JANUVIA 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 JANUVIA, ask your doctor or pharmacist.

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

**Serious side effects can happen in people taking JANUVIA**, including inflammation of the pancreas (pancreatitis) which may be severe and lead to death. Certain medical problems make you more likely to get pancreatitis.

**Before you start taking JANUVIA:**

Tell your doctor if you have ever had

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

Stop taking JANUVIA 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.

**What is JANUVIA?**

- JANUVIA is a prescription medicine used along with diet and exercise to lower blood sugar in adults with type 2 diabetes.
- JANUVIA is not for people with type 1 diabetes.
- JANUVIA 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 JANUVIA.
- It is not known if JANUVIA is safe and effective when used in children under 18 years of age.

**Who should not take JANUVIA?**

**Do not take JANUVIA if:**

- you are allergic to any of the ingredients in JANUVIA. See the end of this Medication Guide for a complete list of ingredients in JANUVIA.

Symptoms of a serious allergic reaction to JANUVIA 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.

**What should I tell my doctor before taking JANUVIA?**

**Before you take JANUVIA, tell your doctor if you:**

- have or have had inflammation of your pancreas (pancreatitis).
- have kidney problems.
- have any other medical conditions.
- are pregnant or plan to become pregnant. It is not known if JANUVIA 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 JANUVIA at any time during your pregnancy, talk with your doctor about how you can join the JANUVIA 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 JANUVIA will pass into your breast milk. Talk with your doctor about the best way to feed your baby if you are taking JANUVIA.

**Tell your doctor about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

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 JANUVIA?**

- Take JANUVIA 1 time each day exactly as your doctor tells you.
- You can take JANUVIA with or without food.
- Your doctor may do blood tests from time to time to see how well your kidneys are working. Your doctor may change your dose of JANUVIA based on the results of your blood tests.
- Your doctor may tell you to take JANUVIA along with other diabetes medicines. Low blood sugar can happen more often when JANUVIA is taken with certain other diabetes medicines. See **“What are the possible side effects of JANUVIA?”**.
- If you miss a dose, take it 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 two doses of JANUVIA at the same time.
- If you take too much JANUVIA, call your doctor or local Poison Control Center right away.
- 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 conditions

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 JANUVIA.
- 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.

#### **What are the possible side effects of JANUVIA?**

##### **Serious side effects have happened in people taking JANUVIA.**

- See "**What is the most important information I should know about JANUVIA?**".
- **Low blood sugar (hypoglycemia).** If you take JANUVIA 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 JANUVIA. Signs and symptoms of low blood sugar may include:
  - headache
  - drowsiness
  - irritability
  - hunger
  - dizziness
  - confusion
  - sweating
  - feeling jittery
  - weakness
  - fast heart beat
- **Serious allergic reactions.** If you have any symptoms of a serious allergic reaction, stop taking JANUVIA and call your doctor right away. See "**Who should not take JANUVIA?**". 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 like JANUVIA, may develop joint pain that can be severe. Call your doctor if you have severe joint pain.

The most common side effects of JANUVIA include upper respiratory infection, stuffy or runny nose and sore throat, and headache.

JANUVIA may have other side effects, including stomach upset and diarrhea, swelling of the hands or legs, when JANUVIA is used with rosiglitazone (Avandia®). Rosiglitazone is another type of diabetes medicine.

These are not all the possible side effects of JANUVIA. 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 JANUVIA?**

Store JANUVIA at 68°F to 77°F (20°C to 25°C).

**Keep JANUVIA and all medicines out of the reach of children.**

#### **General information about the use of JANUVIA**

Medicines are sometimes prescribed for purposes that are not listed in Medication Guides. Do not use JANUVIA for a condition for which it was not prescribed. Do not give JANUVIA 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 JANUVIA. If you would like to know more information, talk with your doctor. You can ask your doctor or pharmacist for additional information about JANUVIA that is written for health professionals. For more information, go to [www.JANUVIA.com](http://www.JANUVIA.com) or call 1-800-622-4477.

#### **What are the ingredients in JANUVIA?**

Active ingredient: sitagliptin

Inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, and sodium stearyl fumarate. The tablet film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, red iron oxide, and 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.

08/2015

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

JANUMET® (sitagliptin and metformin HCl) tablets  
Initial U.S. Approval: 2007

### WARNING: LACTIC ACIDOSIS

See full prescribing information for complete boxed warning.

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

### RECENT MAJOR CHANGES

Warnings and Precautions

Severe and Disabling Arthralgia (5.15)

08/2015

### INDICATIONS AND USAGE

JANUMET is a dipeptidyl peptidase-4 (DPP-4) inhibitor and biguanide combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both sitagliptin and metformin is appropriate. (1, 14)

Important Limitations of Use:

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

### DOSAGE AND ADMINISTRATION

- Individualize the starting dose of JANUMET based on the patient's current regimen. (2.1)
- May adjust the dosing based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 100 mg sitagliptin and 2000 mg metformin. (2.1)
- JANUMET should be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects due to metformin. (2.1)

### DOSAGE FORMS AND STRENGTHS

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

### CONTRAINDICATIONS

- Renal dysfunction, e.g., serum creatinine  $\geq 1.5$  mg/dL [males],  $\geq 1.4$  mg/dL [females] or abnormal creatinine clearance. (4, 5.1, 5.4)
- Metabolic acidosis, including diabetic ketoacidosis. (4, 5.1)
- History of a serious hypersensitivity reaction to JANUMET or sitagliptin (one of the components of JANUMET), such as anaphylaxis or angioedema. (5.14, 6.2)

### WARNINGS AND PRECAUTIONS

- Lactic acidosis: Warn against excessive alcohol intake. JANUMET is not recommended in hepatic impairment and is contraindicated in renal impairment. Ensure normal renal function before initiating and at least annually thereafter. (4, 5.1, 5.3, 5.4, 5.6)

- Temporarily discontinue JANUMET in patients undergoing radiologic studies with intravascular administration of iodinated contrast materials or any surgical procedures necessitating restricted intake of food or fluids. (5.1, 5.4, 5.7, 5.11)
- There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. If pancreatitis is suspected, promptly discontinue JANUMET. (5.2)
- There have been postmarketing reports of acute renal failure, sometimes requiring dialysis. Before initiating JANUMET and at least annually thereafter, assess renal function and verify as normal. (4, 5.1, 5.4, 5.10, 6.2)
- Vitamin B<sub>12</sub> deficiency: Metformin may lower Vitamin B<sub>12</sub> levels. Measure hematologic parameters annually. (5.5, 6.1)
- When used with an insulin secretagogue (e.g., sulfonylurea) or with insulin, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia. (2.1, 5.9)
- There have been postmarketing reports of serious allergic and hypersensitivity reactions in patients treated with sitagliptin (one of the components of JANUMET), such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. In such cases, promptly stop JANUMET, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes. (5.14, 6.2)
- 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. (5.15)
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with JANUMET or any other anti-diabetic drug. (5.16)

### ADVERSE REACTIONS

- The most common adverse reactions reported in  $\geq 5\%$  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  $\geq 5\%$  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  $\geq 5\%$  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

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

### USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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## FULL PRESCRIBING INFORMATION

### WARNING: LACTIC ACIDOSIS

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

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

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

If acidosis is suspected, JANUMET should be discontinued and the patient hospitalized immediately. [See *Warnings and Precautions (5.1)*.]

## 1 INDICATIONS AND USAGE

JANUMET is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both sitagliptin and metformin is appropriate. [See *Clinical Studies (14)*.]

### *Important Limitations of Use*

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

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

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Dosing

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

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

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

50 mg sitagliptin/500 mg metformin hydrochloride

50 mg sitagliptin/1000 mg metformin hydrochloride.

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

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

### *Patients treated with an insulin secretagogue or insulin*

Coadministration of JANUMET with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia [see *Warnings and Precautions (5.9)*].

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

### 3 DOSAGE FORMS AND STRENGTHS

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

### 4 CONTRAINDICATIONS

JANUMET (sitagliptin and metformin HCl) is contraindicated in patients with:

- Renal impairment (e.g., serum creatinine levels greater than or equal to 1.5 mg/dL for men, greater than or equal to 1.4 mg/dL for women or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia [see *Warnings and Precautions (5.1)*].
- Hypersensitivity to metformin hydrochloride.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
- History of a serious hypersensitivity reaction to JANUMET or sitagliptin (one of the components of JANUMET), such as anaphylaxis or angioedema. [See *Warnings and Precautions (5.14)*; *Adverse Reactions (6.2)*.]

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Lactic Acidosis

##### *Metformin hydrochloride*

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

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal impairment, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking metformin, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure [see *Warnings and Precautions (5.4, 5.6, 5.7, 5.11)*].

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur [see

*Warnings and Precautions (5.12)*]. Metformin should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking metformin do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling [*see Warnings and Precautions (5.8, 5.13)*].

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

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery [*see Contraindications (4); Warnings and Precautions (5.6, 5.7, 5.10, 5.11, 5.12)*].

## **5.2 Pancreatitis**

There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking JANUMET. After initiation of JANUMET, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, JANUMET 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.

## **5.3 Impaired Hepatic Function**

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

## **5.4 Assessment of Renal Function**

Metformin and sitagliptin are known to be substantially excreted by the kidney.

### *Metformin hydrochloride*

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

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

### *Sitagliptin*

There have been postmarketing reports of worsening renal function, including acute renal failure, sometimes requiring dialysis. Before initiation of therapy with JANUMET and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, particularly in elderly patients, renal function should be assessed more frequently and JANUMET 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 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 Alcohol Intake

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving JANUMET.

## 5.7 Surgical Procedures

Use of JANUMET should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

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

A patient with type 2 diabetes previously well controlled on JANUMET 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 must be stopped immediately and other appropriate corrective measures initiated.

## 5.9 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 *Dosage and Administration (2.1)*].

### *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.

## 5.10 Concomitant Medications Affecting Renal Function or Metformin Disposition

Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion [see *Drug Interactions (7.2)*], should be used with caution.

## 5.11 Radiologic Studies with Intravascular Iodinated Contrast Materials

Intravascular contrast studies with iodinated materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials) can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin [see *Contraindications (4)*]. Therefore, in patients in whom any such study is planned, JANUMET should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstated only after renal function has been re-evaluated and found to be normal.

## 5.12 Hypoxic States

Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on JANUMET therapy, the drug should be promptly discontinued.

## 5.13 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 and temporarily administer insulin. JANUMET may be reinstated after the acute episode is resolved.

## 5.14 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, one of the components of JANUMET. 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, assess for other potential causes for the event, and institute alternative treatment for diabetes. [See *Adverse Reactions (6.2).*]

Angioedema has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors. Use caution in a patient with a history of angioedema with another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with JANUMET.

### 5.15 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.

### 5.16 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with JANUMET or any other anti-diabetic drug.

## 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 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 were coadministered to patients with type 2 diabetes inadequately controlled on diet and exercise.

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

	Number of Patients (%)			
	Placebo	Sitagliptin 100 mg once daily	Metformin 500 mg/ Metformin 1000 mg twice daily <sup>†</sup>	Sitagliptin 50 mg twice daily + Metformin 500 mg/ Metformin 1000 mg twice daily <sup>†</sup>
	<b>N = 176</b>	<b>N = 179</b>	<b>N = 364<sup>†</sup></b>	<b>N = 372<sup>†</sup></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.

<sup>†</sup> 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 Alone*

In a 24-week placebo-controlled trial of sitagliptin 100 mg administered once daily added to a twice daily metformin regimen, there were no adverse reactions reported regardless of investigator assessment of causality in  $\geq 5\%$  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, 1.9%; placebo and metformin, 2.5%).

### *Gastrointestinal Adverse Reactions*

The incidences of pre-selected gastrointestinal adverse experiences in patients treated with sitagliptin and metformin were similar to those reported for patients treated with metformin 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**

	Number of Patients (%)					
	Study of Sitagliptin and Metformin in Patients Inadequately Controlled on Diet and Exercise				Study of Sitagliptin Add-on in Patients Inadequately Controlled on Metformin Alone	
	Placebo	Sitagliptin 100 mg once daily	Metformin 500 mg/ Metformin 1000 mg twice daily*	Sitagliptin 50 mg twice daily + Metformin 500 mg/ Metformin 1000 mg twice daily*	Placebo and Metformin ≥1500 mg daily	Sitagliptin 100 mg once daily and Metformin ≥1500 mg daily
	N = 176	N = 179	N = 364	N = 372	N = 237	N = 464
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 <sup>†</sup>	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.

<sup>†</sup> Abdominal discomfort was included in the analysis of abdominal pain in the study of initial therapy.

#### *Sitagliptin in Combination with Metformin 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 and glimepiride (sitagliptin, N=116; placebo, N=113), the adverse reactions reported regardless of investigator assessment of causality in ≥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 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 and rosiglitazone (sitagliptin, N=181; placebo, N=97), the adverse reactions reported regardless of investigator assessment of causality through Week 18 in ≥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 ≥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 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 and insulin (sitagliptin, N=229; placebo, N=233), the only adverse reaction reported regardless of investigator assessment of causality in ≥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 ≤70 mg/dL. When the combination of sitagliptin and metformin 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 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 Coadministered with Glimepiride or Insulin**

<b>Add-On to Glimepiride + Metformin (24 weeks)</b>	<b>Sitagliptin 100 mg + Metformin + Glimepiride</b>	<b>Placebo + Metformin + 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 (24 weeks)</b>	<b>Sitagliptin 100 mg + Metformin + Insulin</b>	<b>Placebo + Metformin + 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 alone, and 1.6% in patients given sitagliptin in combination with metformin. In patients with type 2 diabetes inadequately controlled on metformin 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 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, no clinically meaningful changes in vital signs or in ECG (including in 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 ≥5% of patients and more commonly than in patients given placebo was nasopharyngitis.

#### *Metformin hydrochloride*

The most common (>5%) established adverse reactions due to initiation of metformin therapy are diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache.

#### *Laboratory Tests*

##### *Sitagliptin*

The incidence of laboratory adverse reactions was similar in patients treated with sitagliptin and metformin (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 JANUMET or sitagliptin, one of the components of JANUMET. These reactions have been reported when JANUMET or sitagliptin have been used alone and/or in combination with other antihyperglycemic agents. 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 (5.14)*]; 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 (5.15)*]; constipation; vomiting; headache; myalgia; pain in extremity; back pain; pruritus.

## **7 DRUG INTERACTIONS**

### **7.1 Carbonic Anhydrase Inhibitors**

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorophenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis. Use these drugs with caution in patients treated with JANUMET, as the risk of lactic acidosis may increase.

### **7.2 Cationic Drugs**

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of JANUMET and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

### **7.3 The 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 the patient should be closely observed to maintain adequate glycemic control.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

*Pregnancy Category B:*

*JANUMET*

There are no adequate and well-controlled studies in pregnant women with JANUMET or its individual components; therefore, the safety of JANUMET in pregnant women is not known. JANUMET should be used during pregnancy only if clearly needed.

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., maintains a registry to monitor the pregnancy outcomes of women exposed to JANUMET while pregnant. Health care providers are encouraged to report any prenatal exposure to JANUMET by calling the Pregnancy Registry at 1-800-986-8999.

No animal studies have been conducted with the combined products in JANUMET to evaluate effects on reproduction. The following data are based on findings in studies performed with sitagliptin or metformin individually.

### *Sitagliptin*

Reproduction studies have been performed in rats and rabbits. Doses of sitagliptin up to 125 mg/kg (approximately 12 times the human exposure at the maximum recommended human dose) did not impair fertility or harm the fetus. There are, however, no adequate and well-controlled studies with sitagliptin in pregnant women.

Sitagliptin administered to pregnant female rats and rabbits from gestation day 6 to 20 (organogenesis) was not teratogenic at oral doses up to 250 mg/kg (rats) and 125 mg/kg (rabbits), or approximately 30 and 20 times human exposure at the maximum recommended human dose (MRHD) of 100 mg/day based on AUC comparisons. Higher doses increased the incidence of rib malformations in offspring at 1000 mg/kg, or approximately 100 times human exposure at the MRHD.

Sitagliptin administered to female rats from gestation day 6 to lactation day 21 decreased body weight in male and female offspring at 1000 mg/kg. No functional or behavioral toxicity was observed in offspring of rats.

Placental transfer of sitagliptin administered to pregnant rats was approximately 45% at 2 hours and 80% at 24 hours postdose. Placental transfer of sitagliptin administered to pregnant rabbits was approximately 66% at 2 hours and 30% at 24 hours.

### *Metformin hydrochloride*

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the maximum recommended human daily dose of 2,000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

### **8.3 Nursing Mothers**

No studies in lactating animals have been conducted with the combined components of JANUMET. In studies performed with the individual components, both sitagliptin and metformin are secreted in the milk of lactating rats. It is not known whether sitagliptin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when JANUMET is administered to a nursing woman.

### **8.4 Pediatric Use**

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

### **8.5 Geriatric Use**

#### *JANUMET*

Because sitagliptin and metformin are substantially excreted by the kidney, and because aging can be associated with reduced renal function, JANUMET should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. [See *Warnings and Precautions (5.1, 5.4); Clinical Pharmacology (12.3).*]

#### *Sitagliptin*

Of the total number of subjects (N=3884) in 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. Metformin should only be used in patients with normal renal function. The initial and maintenance dosing of metformin should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dose adjustment should be based on a careful assessment of renal function. [See *Contraindications (4); Warnings and Precautions (5.4); Clinical Pharmacology (12.3).*]

## 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*

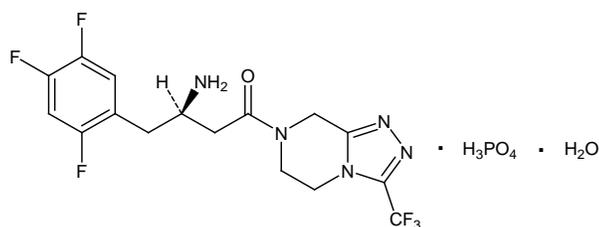
Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin 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 overdose is suspected.

## 11 DESCRIPTION

JANUMET (sitagliptin and metformin HCl) tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: sitagliptin and metformin hydrochloride.

### *Sitagliptin*

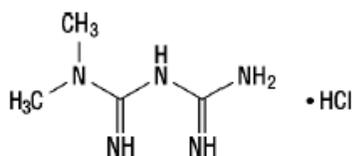
Sitagliptin is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme. Sitagliptin is present in JANUMET tablets in the form of sitagliptin phosphate monohydrate. Sitagliptin phosphate monohydrate is described chemically as 7-[(3*R*)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyrazine 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 not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Metformin 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

JANUMET is available for oral administration as tablets containing 64.25 mg sitagliptin phosphate monohydrate and metformin hydrochloride equivalent to: 50 mg sitagliptin as free base and 500 mg metformin hydrochloride (JANUMET 50 mg/500 mg) or 1000 mg metformin hydrochloride (JANUMET 50 mg/1000 mg). Each film-coated tablet of JANUMET contains the following inactive ingredients: microcrystalline cellulose, polyvinylpyrrolidone, sodium lauryl sulfate, and sodium stearyl fumarate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, red iron oxide, and black iron oxide.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

#### JANUMET

JANUMET combines two antidiabetic medications with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class.

#### Sitagliptin

Sitagliptin is a DPP-4 inhibitor, which is believed to exert 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 an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances [see *Warnings and Precautions* (5.9)]) 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

##### General

In patients with type 2 diabetes, 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.

#### *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.

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

#### *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 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*

The results of a bioequivalence study in healthy subjects demonstrated that the JANUMET (sitagliptin and metformin HCl) 50 mg/500 mg and 50 mg/1000 mg combination tablets are bioequivalent to coadministration of corresponding doses of sitagliptin (JANUVIA®) and metformin hydrochloride as individual tablets.

#### *Absorption*

##### *Sitagliptin*

The absolute bioavailability of sitagliptin is approximately 87%. 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 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. 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*

The apparent volume of distribution (V/F) of metformin following single oral doses of metformin hydrochloride tablets 850 mg averaged  $654 \pm 358$  L. Metformin is negligibly bound to plasma proteins, in

contrast to sulfonylureas, which are more than 90% protein bound. 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.

#### *Metabolism*

##### *Sitagliptin*

Approximately 79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination.

Following a [<sup>14</sup>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) nor biliary excretion.

#### *Excretion*

##### *Sitagliptin*

Following administration of an oral [<sup>14</sup>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. 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.

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, which may also be involved in mediating the renal elimination of sitagliptin. However, cyclosporine, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin.

##### *Metformin hydrochloride*

Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. 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.

#### *Specific Populations*

##### *Renal Impairment*

##### *JANUMET*

JANUMET should not be used in patients with renal impairment [see *Contraindications (4); Warnings and Precautions (5.4)*].

##### *Sitagliptin*

An approximately 2-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal impairment, and an approximately 4-fold increase was observed in patients with severe renal impairment including patients with ESRD on hemodialysis, as compared to normal healthy control subjects.

##### *Metformin hydrochloride*

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

## *Hepatic Impairment*

### *Sitagliptin*

In patients with moderate hepatic impairment (Child-Pugh score 7 to 9), mean AUC and  $C_{\max}$  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).

### *Metformin hydrochloride*

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

## *Gender*

### *Sitagliptin*

Gender had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

### *Metformin hydrochloride*

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

## *Geriatric*

### *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  $C_{\max}$  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.

As is true for all patients, JANUMET treatment should not be initiated in geriatric patients unless measurement of creatinine clearance demonstrates that renal function is normal [see *Warnings and Precautions* (5.1, 5.4)].

## *Pediatric*

No studies with JANUMET have been performed in pediatric patients.

## *Race*

### *Sitagliptin*

Race had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of available pharmacokinetic data, including subjects of white, Hispanic, black, Asian, and other racial groups.

### *Metformin hydrochloride*

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

## Body Mass Index (BMI)

### Sitagliptin

Body mass index had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

### Drug Interactions

#### Sitagliptin and Metformin hydrochloride

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 have not been performed; however, such studies have been conducted with the individual components of JANUMET (sitagliptin and metformin hydrochloride).

### 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-glycoprotein substrate, but does not inhibit p-glycoprotein 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

**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 <sup>†</sup>	C <sub>max</sub>
<b>No dosing adjustments required for the following:</b>					
Digoxin	0.25 mg <sup>‡</sup> once daily for 10 days	100 mg <sup>‡</sup> once daily for 10 days	Digoxin	1.11 <sup>§</sup>	1.18
Glyburide	1.25 mg	200 mg <sup>‡</sup> once daily for 6 days	Glyburide	1.09	1.01
Simvastatin	20 mg	200 mg <sup>‡</sup> once daily for 5 days	Simvastatin	0.85 <sup>¶</sup>	0.80
			Simvastatin Acid	1.12 <sup>¶</sup>	1.06
Rosiglitazone	4 mg	200 mg <sup>‡</sup> once daily for 5 days	Rosiglitazone	0.98	0.99
Warfarin	30 mg single dose on day 5	200 mg <sup>‡</sup> 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 <sup>‡</sup> 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

\* 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>.

**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>
<b>No dosing adjustments required for the following:</b>					
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>.

**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>
<b>No dosing adjustments required for the following:</b>					
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>.

§ Ratio of arithmetic means, p value of difference <0.05.

¶ GLUMETZA (metformin hydrochloride extended-release tablets) 500 mg.

# 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>
<b>No dosing adjustments required for the following:</b>					
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>Cationic drugs eliminated by renal tubular secretion may reduce metformin elimination: use with caution. [See Warnings and Precautions (5.10) and Drug Interactions (7.2).]</b>					
Cimetidine	400 mg	850 mg	Metformin	1.40	1.61
<b>Carbonic anhydrase inhibitors may cause metabolic acidosis: use with caution. [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

No animal studies have been conducted with the combined products in JANUMET 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 rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately four times 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 mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There was no evidence of a mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative. Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

## 14 CLINICAL STUDIES

The coadministration of sitagliptin and metformin has been studied in patients with type 2 diabetes inadequately controlled on diet and exercise and in combination with other antihyperglycemic agents.

None of the clinical efficacy studies described below was conducted with JANUMET; however, bioequivalence of JANUMET with coadministered sitagliptin and metformin hydrochloride tablets was demonstrated.

### **Sitagliptin and Metformin 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 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 twice daily, or 50 mg of sitagliptin twice daily in combination with 500 mg or 1000 mg of metformin twice daily. Patients who failed to meet specific glycemic goals during the study were treated with glyburide (glibenclamide) rescue.

Sitagliptin and metformin coadministration provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo, to metformin alone, and to sitagliptin alone (Table 8, Figure 1). Mean reductions from baseline in A1C were generally greater for patients with higher baseline A1C values. 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 500 mg bid, -1.1%; metformin 1000 mg bid, -1.2%; sitagliptin 50 mg bid with metformin 500 mg bid, -1.6%; sitagliptin 50 mg bid with metformin 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 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, Alone and in Combination in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise\***

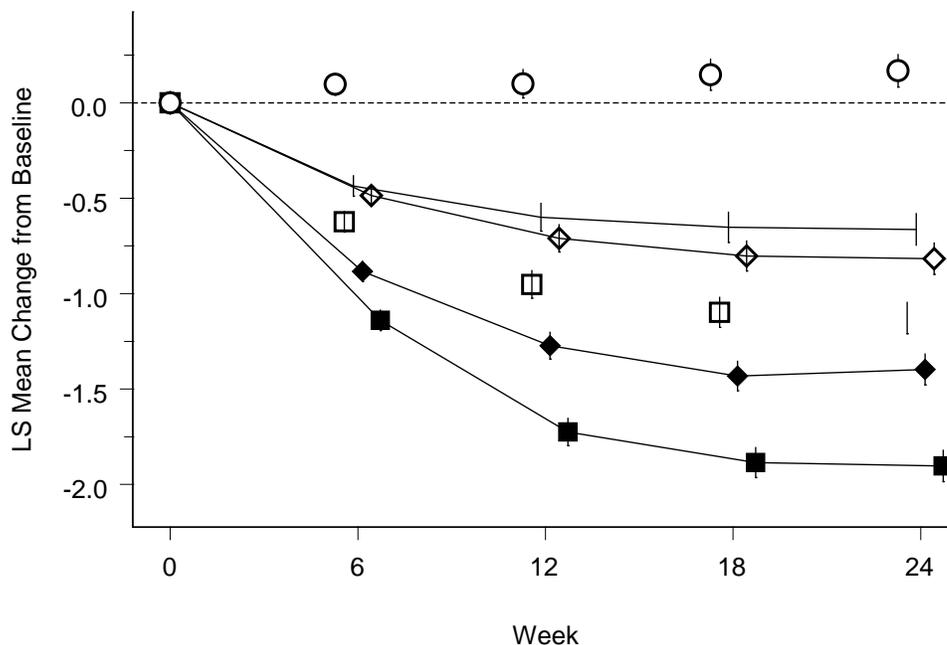
	Placebo	Sitagliptin 100 mg once daily	Metformin 500 mg twice daily	Metformin 1000 mg twice daily	Sitagliptin 50 mg twice daily + Metformin 500 mg twice daily	Sitagliptin 50 mg twice daily + Metformin 1000 mg twice daily
<b>A1C (%)</b>	<b>N = 165</b>	<b>N = 175</b>	<b>N = 178</b>	<b>N = 177</b>	<b>N = 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, Alone and in Combination in Patients with Type 2 Diabetes Inadequately Controlled with Diet and Exercise\***



- Placebo
- Sitagliptin 100 mg q.d.
- ◇ Metformin 500 mg b.i.d.
- Metformin 1000 mg b.i.d.
- ◆ Sitagliptin 50 mg b.i.d. + Metformin 500 mg b.i.d.
- Sitagliptin 50 mg b.i.d. + Metformin 1000 mg b.i.d.

\* All Patients Treated 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 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. Patients already on metformin (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 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 (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, sitagliptin provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo with metformin (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\***

	<b>Sitagliptin 100 mg once daily + Metformin</b>	<b>Placebo + Metformin</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 (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 (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 (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 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. Patients entered a run-in treatment period on glimepiride (≥4 mg per day) alone or glimepiride in combination with metformin (≥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 and glimepiride had significant improvements in A1C and FPG compared to patients receiving placebo with metformin 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* (5.9); *Adverse Reactions* (6.1).]

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

	<b>Sitagliptin 100 mg + Metformin and Glimepiride</b>	<b>Placebo + Metformin 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 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 and rosiglitazone. Patients on dual therapy with metformin  $\geq 1500$  mg/day and rosiglitazone  $\geq 4$  mg/day or with metformin  $\geq 1500$  mg/day and pioglitazone  $\geq 30$  mg/day (switched to rosiglitazone  $\geq 4$  mg/day) entered a dose-stable run-in period of 6 weeks. Patients on other dual therapy were switched to metformin  $\geq 1500$  mg/day and rosiglitazone  $\geq 4$  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 and rosiglitazone, sitagliptin provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo with metformin 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 and Rosiglitazone\***

	Week 18	
	Sitagliptin 100 mg + Metformin + Rosiglitazone	Placebo + Metformin + Rosiglitazone
<b>A1C (%)</b>	<b>N = 176</b>	<b>N = 93</b>
Baseline (mean)	8.8	8.7
Change from baseline (adjusted mean <sup>†</sup> )	-1.0	-0.4
Difference from placebo + rosiglitazone + metformin (adjusted mean <sup>†</sup> ) (95% CI)	-0.7 <sup>‡</sup> (-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 <sup>†</sup> )	-30	-11
Difference from placebo + rosiglitazone + metformin (adjusted mean <sup>†</sup> ) (95% CI)	-18 <sup>‡</sup> (-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 <sup>†</sup> )	-59	-21
Difference from placebo + rosiglitazone + metformin (adjusted mean <sup>†</sup> ) (95% CI)	-39 <sup>‡</sup> (-51, -26)	

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

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

<sup>‡</sup> 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 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. Patients entered a 2-week, single-blind run-in treatment period on pre-mixed, long-acting, or intermediate-acting insulin, with or without metformin (≥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, 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 and insulin had significant improvements in A1C, FPG and 2-hour PPG compared to patients receiving placebo with metformin and insulin (Table 12). The adjusted mean change from baseline in body weight was -0.3 kg in patients receiving sitagliptin with metformin and insulin and -0.2 kg in patients receiving placebo with metformin and insulin. There was an increased rate of hypoglycemia in patients treated with sitagliptin. [See *Warnings and Precautions (5.9); Adverse Reactions (6.1).*]

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

	<b>Sitagliptin 100 mg + Metformin + Insulin</b>	<b>Placebo + Metformin + Insulin</b>
<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.

† 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.

‡ Treatment by insulin stratum interaction was not significant ( $p > 0.10$ ).

§  $p < 0.001$  compared to placebo.

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

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 monotherapy (dose of  $\geq 1500$  mg per day) which included washout of medications other than metformin, 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%).

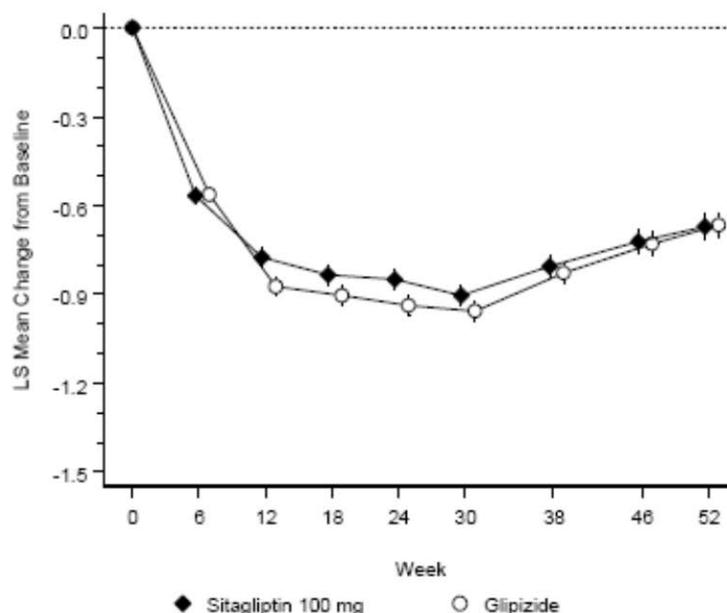
**Table 13: Glycemic Parameters in a 52-Week Study Comparing Sitagliptin to Glipizide as Add-On Therapy in Patients Inadequately Controlled on Metformin (Intent-to-Treat Population)\***

	<b>Sitagliptin 100 mg + Metformin</b>	<b>Glipizide + Metformin</b>
<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 (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. 6747 — Tablets JANUMET, 50 mg/500 mg, are light pink, capsule-shaped, film-coated tablets with "575" debossed on one side. They are supplied as follows:

NDC 0006-0575-61 unit-of-use bottles of 60

NDC 0006-0575-62 unit-of-use bottles of 180

NDC 0006-0575-52 unit dose blister packages of 50

NDC 0006-0575-82 bulk bottles of 1000.

No. 6749 — Tablets JANUMET, 50 mg/1000 mg, are red, capsule-shaped, film-coated tablets with “577” debossed on one side. They are supplied as follows:

NDC 0006-0577-61 unit-of-use bottles of 60

NDC 0006-0577-62 unit-of-use bottles of 180

NDC 0006-0577-52 unit dose blister packages of 50

NDC 0006-0577-82 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.]

## 17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Medication Guide).

### 17.1 Instructions

Patients should be informed of the potential risks and benefits of JANUMET 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 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 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.

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

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

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 and contact their physician if persistent severe abdominal pain occurs [see Warnings and Precautions (5.2)].

Patients should be informed that the incidence of hypoglycemia is increased when JANUMET 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. 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 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 (5.15)].

Patients should be informed that the tablets must never be split or divided before swallowing.

Physicians should instruct their patients to read the Medication Guide before starting JANUMET 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® (JAN-you-met)**  
**(sitagliptin and metformin hydrochloride)**  
**Tablets**

Read this Medication Guide carefully before you start taking JANUMET 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, ask your doctor or pharmacist.

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

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

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

**Stop taking JANUMET and call your doctor right away if you get any of the following symptoms, which could be signs of lactic acidosis.**

You:

- feel very weak or tired.
- have unusual (not normal) muscle pain.
- have trouble breathing.
- have unusual sleepiness or sleep longer than usual.
- have sudden stomach or intestinal problems with nausea and vomiting or diarrhea.
- feel cold, especially in your arms and legs.
- feel dizzy or lightheaded.
- have a slow or irregular heartbeat.

**You have a higher chance of getting lactic acidosis if you:**

- have kidney problems. People whose kidneys are not working properly should not take JANUMET.
- have liver problems.
- have congestive heart failure that requires treatment with medicines.
- 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 certain x-ray tests with dyes or contrast agents that are injected into your body.
- have surgery.
- have a heart attack, severe infection, or stroke.

**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:**

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 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.

**What is JANUMET?**

- JANUMET is a prescription medicine that contains 2 prescription diabetes medicines, sitagliptin (JANUVIA®) and metformin. JANUMET can be used along with diet and exercise to lower blood sugar in adults with type 2 diabetes.
- JANUMET is not for people with type 1 diabetes.
- JANUMET 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.
- It is not known if JANUMET is safe and effective when used in children under 18 years of age.

**Who should not take JANUMET?**

**Do not take JANUMET if:**

- your kidneys are not working properly.
- you are allergic to any of the ingredients in JANUMET. See the end of this Medication Guide for a complete list of ingredients in JANUMET.

Symptoms of a serious allergic reaction to JANUMET 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?**".

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

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

- have or have had inflammation of your pancreas (pancreatitis).
- have 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 will need to be stopped for a short time. Talk to your doctor about when you should stop JANUMET and when you should start JANUMET again. See **“What is the most important information I should know about JANUMET?”**.
- have any other medical conditions.
- are pregnant or plan to become pregnant. It is not known if JANUMET 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 at any time during your pregnancy, talk with your doctor about how you can join the JANUMET 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 will pass into your breast milk. Talk with your doctor about the best way to feed your baby if you are taking JANUMET.

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

- Take JANUMET exactly as your doctor tells you. Your doctor will tell you how many JANUMET tablets to take and when you should take them.
- Your doctor may change your dose of JANUMET if needed.
- Your doctor may tell you to take JANUMET along with certain other diabetes medicines. Low blood sugar (hypoglycemia) can happen more often when JANUMET is taken with certain other diabetes medicines. See **“What are the possible side effects of JANUMET?”**.
- Take JANUMET with meals to help to lower your chance of having an upset stomach.
- Do not break or cut JANUMET tablets before swallowing. If you cannot swallow JANUMET tablets whole, tell your doctor.
- Continue to take JANUMET as long as your doctor tells you.
- If you take too much JANUMET, call your doctor or local Poison Control Center right away.
- If you miss a dose, take it 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 at the same time.
- You may need to stop taking JANUMET 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?”** and **“What should I tell my doctor before taking JANUMET?”**.
- 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.
- 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.

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

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

- See **“What is the most important information I should know about JANUMET?”**.
- **Low blood sugar (hypoglycemia).** If you take JANUMET 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. Signs and symptoms of low blood sugar may include:

- headache
- drowsiness
- irritability
- hunger
- dizziness
- confusion
- sweating
- feeling jittery
- weakness
- fast heart beat

• **Serious allergic reactions.** If you have any symptoms of a serious allergic reaction, stop taking JANUMET and call your doctor right away. See "**Who should not take JANUMET?**". 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, may develop joint pain that can be severe. Call your doctor if you have severe joint pain.

The most common side effects of JANUMET include:

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

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

These are not all the possible side effects of JANUMET. 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?**

Store JANUMET at 68°F to 77°F (20°C to 25°C).

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

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

Medicines are sometimes prescribed for purposes other than those listed in Medication Guides. Do not use JANUMET for a condition for which it was not prescribed. Do not give JANUMET 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. If you would like to know more information, talk with your doctor. You can ask your doctor or pharmacist for additional information about JANUMET that is written for health care professionals. For more information go to [www.janumet.com](http://www.janumet.com) or call 1-800-622-4477.

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

**Active ingredients:** sitagliptin and metformin

**Inactive ingredients:** microcrystalline cellulose, polyvinylpyrrolidone, sodium lauryl sulfate, and sodium stearyl fumarate. The tablet film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, red iron oxide, and black 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.

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