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 ----------

Indications and Usage	
Monotherapy and Combination Therapy (1.1)	10/2007
Important Limitations of Use (1.2)	10/2007
Dosage and Administration	
Recommended Dosing (2.1)	10/2007
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Contraindications (4)	10/2007
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Use with Medications Known to Cause Hypoglycemia (5.2)	10/2007
Hypersensitivity Reactions (5.3)	10/2007
Macrovascular Outcomes (5.4)	7/2008

---------- 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 combination with insulin. (1.2)

---------- 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 CrCl ≥30 to <50 mL/min ~Serum Cr levels [mg/dL] Men: >1.7– ≤3.0; Women: >1.5– ≤2.5	Severe and ESRD 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 (5.3, 6.2)

---------- WARNINGS AND PRECAUTIONS ----------
- 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, 5.1)
- When used with a sulfonylurea, a lower dose of sulfonylurea may be required to reduce the risk of hypoglycemia. (2.3, 5.2)
- 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. (5.3, 6.2)
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with JANUVIA or any other anti-diabetic drug. (5.4)

---------- ADVERSE REACTIONS ----------
Adverse reactions reported in ≥5% of patients treated with JANUVIA and more commonly than in patients treated with placebo are: upper respiratory tract infection, nasopharyngitis and headache. Hypoglycemia was also reported more commonly in patients treated with the combination of JANUVIA and sulfonylurea, with or without metformin, than in patients given the combination of placebo and sulfonylurea, with or without metformin. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Merck & Co., Inc. at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- 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 FDA-approved patient labeling.

Revised: 7/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Monotherapy and Combination Therapy

JANUVIA[1] 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 combination with insulin.

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] ≥50 mL/min, approximately corresponding to serum creatinine levels of ≤1.7 mg/dL in men and ≤1.5 mg/dL in women), no dosage adjustment for JANUVIA is required.

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

For patients with severe renal insufficiency (CrCl <30 mL/min, approximately corresponding to serum creatinine levels of >3.0 mg/dL in men and >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 hemodialysis.

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).]*

2.3 Concomitant Use with a Sulfonylurea

When JANUVIA is used in combination with a sulfonylurea, a lower dose of sulfonylurea may be required to reduce the risk of hypoglycemia. *[See Warnings and Precautions (5.2).]*

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 (5.3) and Adverse Reactions (6.2).]*

5 WARNINGS AND PRECAUTIONS

5.1 Use in Patients with Renal Insufficiency

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).]*

5.2 Use with Medications Known to Cause Hypoglycemia

As is typical with other antihyperglycemic agents used in combination with a sulfonylurea, when JANUVIA was used in combination with a sulfonylurea, a class of medications known to cause

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hypoglycemia, the incidence of hypoglycemia was increased over that of placebo. *[See Adverse Reactions (6.1).]* Therefore, a lower dose of sulfonylurea may be required to reduce the risk of hypoglycemia. *[See Dosage and Administration (2.3).]*

5.3 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. 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. 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).]*

5.4 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 or pioglitazone, 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 1); 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. Three 24-week, placebo-controlled add-on combination therapy studies, one with metformin, one with pioglitazone, and one with glimepiride with or without metformin, were also conducted. In addition to a stable dose of metformin, pioglitazone, glimepiride, or glimepiride and metformin, patients whose diabetes was not adequately controlled were given either JANUVIA 100 mg daily or placebo. The adverse reactions, reported regardless of investigator assessment of causality in ≥5% of patients treated with JANUVIA 100 mg daily as monotherapy, JANUVIA in combination with pioglitazone, or JANUVIA in combination with glimepiride, with or without metformin, and more commonly than in patients treated with placebo, are shown in Table 1.

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Table 1
Placebo-Controlled Clinical Studies of JANUVIA Monotherapy or Add-on Combination Therapy with Pioglitazone or Glimepiride +/- Metformin: Adverse Reactions Reported in ≥5% of Patients and More Commonly than in Patients Given Placebo, Regardless of Investigator Assessment of Causality†

	Number of Patients (%)	
Monotherapy	**JANUVIA 100 mg**	**Placebo**
	N = 443	N = 363
Nasopharyngitis	23 (5.2)	12 (3.3)
Combination with Pioglitazone	**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 Glimepiride (+/- Metformin)	**JANUVIA 100 mg + Glimepiride (+/- Metformin)**	**Placebo + Glimepiride (+/- Metformin)**
	N = 222	N = 219
Hypoglycemia	27 (12.2)	4 (1.8)
Nasopharyngitis	14 (6.3)	10 (4.6)
Headache	13 (5.9)	5 (2.3)

† Intent to treat population

In the 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 ≥5% of patients and more commonly than in patients given placebo.

In the prespecified 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 in patients treated with JANUVIA 100 mg was similar to placebo (1.2% vs 0.9%). Adverse reactions of hypoglycemia were based on all reports of hypoglycemia; a concurrent glucose measurement was not required. 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 ≥5% of patients are shown in Table 2. The incidence of hypoglycemia 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.

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 ††**	**Sitagliptin 50 mg bid + Metformin 500 or 1000 mg bid ††**
	N = 176	N = 179	N = 364††	N = 372††
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.
†† Data pooled for the patients given the lower and higher doses of metformin.

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

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

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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

The following additional adverse reactions have been identified during postapproval use of JANUVIA. 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 include anaphylaxis, angioedema, rash, urticaria, and exfoliative skin conditions including Stevens-Johnson syndrome. *[See Warnings and Precautions (5.3).]*

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 co-administration 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 & 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 (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

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