

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-995**

**APPROVED LABELING**

**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 phosphate) Tablets**  
Initial U.S. Approval: 200X

**INDICATIONS AND USAGE**

JANUVIA is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus (type 2 diabetes). JANUVIA is indicated for:

- Monotherapy (1.1)
- Combination therapy with metformin or a peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) agonist (e.g., thiazolidinediones) when the single agent does not provide adequate glycemic control. (1.2)

**Important Limitations of Use:** JANUVIA should not be used in patients with type 1 diabetes mellitus (type 1 diabetes) or for the treatment of diabetic ketoacidosis. (1.3)

**DOSAGE AND ADMINISTRATION**

The recommended dose of JANUVIA is 100 mg once daily as monotherapy or as combination therapy with metformin or a PPAR $\gamma$  agonist (e.g., thiazolidinediones). (2.1)

JANUVIA can be taken with or without food. (2.1)

Dosage Adjustment in Patients With Moderate, Severe and End Stage Renal Disease (ESRD) (2.2)	
50 mg once daily Moderate	25 mg once daily 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

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**DOSAGE FORMS AND STRENGTHS**

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

**CONTRAINDICATIONS**

None. (4)

**WARNINGS AND PRECAUTIONS**

A dosage adjustment is recommended in patients with moderate renal insufficiency and in patients with severe renal insufficiency or with ESRD requiring hemodialysis or peritoneal dialysis. 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. (2.2, 5)

**ADVERSE REACTIONS**

The most common 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. (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](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)

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

Revised: X/200X

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**FULL PRESCRIBING INFORMATION****1 INDICATIONS AND USAGE****1.1 Monotherapy**

JANUVIA<sup>1</sup> is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.

## 1.2 Combination Therapy

JANUVIA is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin or a PPAR $\gamma$  agonist (e.g., thiazolidinediones) when the single agent alone, with diet and exercise, does not provide adequate glycemic control.

## 1.3 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.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Dosing

The recommended dose of JANUVIA is 100 mg once daily as monotherapy or as combination therapy with metformin or a PPAR $\gamma$  agonist (e.g., thiazolidinediones). JANUVIA can be taken with or without food.

### 2.2 Patients with Renal Insufficiency

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

For patients with moderate renal insufficiency (CrCl  $\geq$ 30 to  $<$ 50 mL/min, approximately corresponding to serum creatinine levels of  $>$ 1.7 to  $\leq$ 3.0 mg/dL in men and  $>$ 1.5 to  $\leq$ 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).]

## 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

None.

## 5 WARNINGS AND PRECAUTIONS

*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).]

*Use with Medications Known to Cause Hypoglycemia:* In clinical trials of JANUVIA as monotherapy and JANUVIA as part of combination therapy with metformin or pioglitazone, rates of hypoglycemia reported with JANUVIA were similar to rates in patients taking placebo. The use of JANUVIA in combination with medications known to cause hypoglycemia, such as sulfonylureas or insulin, has not been adequately studied.

## 6 ADVERSE REACTIONS

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.

### 6.1 Clinical Trials Experience

In controlled clinical studies as both monotherapy and combination therapy, the overall incidence of adverse reactions with JANUVIA was similar to that reported with placebo. Discontinuation of therapy due to clinical adverse reactions was also 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. Two 24-week, placebo-controlled combination studies, one with metformin and one with pioglitazone, were also conducted. In addition to a stable dose of metformin or pioglitazone, 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  $\geq 5\%$  of patients treated with JANUVIA 100 mg daily as monotherapy or in combination with pioglitazone and more commonly than in patients treated with placebo, are shown in Table 1.

**Table 1**  
**Placebo-Controlled Clinical Studies of JANUVIA Monotherapy or Combination with Pioglitazone:**  
**Adverse Reactions Reported in  $\geq 5\%$  of Patients and More Commonly than in Patients**  
**Given Placebo, Regardless of Investigator Assessment of Causality<sup>†</sup>**

Monotherapy	Number of Patients (%)	
	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)

<sup>†</sup> Intent to treat population

In patients receiving JANUVIA in combination 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.

The overall incidence of hypoglycemia in patients treated with JANUVIA 100 mg was similar to placebo (1.2% vs 0.9%). 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%).

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

#### Laboratory Tests

The incidence of laboratory adverse reactions in patients treated with JANUVIA 100 mg was 8.2% compared to 9.8% in patients treated with placebo. Across clinical 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 an increase in neutrophils. This observation was seen in most but not all studies. This change in laboratory parameters 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.

## 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 have not been established.

### 8.5 Geriatric Use

Of the total number of subjects (N=3884) in 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 humans.

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.

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