Information Requested by Ms. Jessica Montealegre

Merck & Co., Inc.
U.S. Human Health
P.O. Box 1000
North Wales, PA 19454-1099
Tel: 800 672 6372
Fax: 800 637 2568



May 16, 2007

Jessica Montealegre, M.D.
Pss World Medical
4345 South Point Boulevard
Jacksonville, FL 32216

Dear Ms. Montealegre:

Our National Service Specialist, Katherine Phelan, R.Ph., has referred your request for information regarding JANUVIA (sitagliptin). Your inquiry concerned receiving a copy of the Material Safety Data Sheet (MSDS) for JANUVIA.

As per your request, enclosed is the Material Safety Data Sheet for JANUVIA.

The above information is supplied to you as a professional service in response to your specific request. Merck & Co., Inc. does not recommend the use of its products in any manner other than as described in the prescribing information. Enclosed for your convenience is prescribing information for JANUVIA.

Sincerely,

Carol B Teutsch

Carol Teutsch, M.D.
Senior Director
Medical Services

Enclosures: Circular, MSDS

Information Requested by Ms. Jessica Montealegre

Public disclosed

SAFETY DATA SHEET

Information Requested by Ms. Jessica Montealegre

1. Product and Company Identification

Manufactured/Supplied by	MERCK & CO., INC. One Merck Drive P.O. Box 100 Whitehouse Station, NJ 08889-0100 (908) 423-1000 Emergency Telephone Number: 1-732-594-5555
Label Name	JANUVIA™ Tablets
Chemical Name	7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahy (trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazinephosphate (1:1) monohydrate
Synonyms	Sitagliptin phosphate monohydrate; MK-0431
Material Product Number	6737 - 25 mg tablets 6738 - 50 mg tablets 6739 - 100 mg tablets
Intended Use	Dipeptidyl peptidase (DPP-4) inhibitor used for the treatment of hyperglycemia in patients with type 2 diabetes mellitus.

2. Composition/Information on Ingredients

Component	Molecular Formula	Molecular weight	CAS Number	Percent (%)
SITAGLIPTIN PHOSPHATE MONOHYDRATE	C16H15F6N5O. H3PO4.H2O	523.32	65467-77-9	31
Inactive Ingredients	- - -	- - -	- - -	69

While this product is exempt from the requirements of the OSHA Hazard Communication Standard and the EU Dangerous Substances Directive, this MSDS contains valuable information critical to the safe handling of the product. This MSDS should be retained and available for employees and other users of the product.

EC Label

Exempt from the EU Dangerous Substances Directive.

3. Hazards Identification

Appearance	25 mg - Pink round film coated tablet 50 mg - Light beige round film coated tablet 100 mg - Beige round film coated tablet
Emergency Overview	CAUTION! FINISHED PHARMACEUTICAL PRODUCT ANTI-DIABETIC AGENT

***** Continued on next page *****

Information Requested by Ms. Jessica Montealegre

	No specific hazard with intact tablets. In case of exposure to crushed or broken tablets avoid contact with skin and eyes and wash thoroughly after handling.
Potential Health Effects	See Section 11 for detailed information.

4. First Aid Measures

Eye Contact	No emergency procedures necessary for intact tablets. If exposure occurs to crushed or broken tablets, immediately flush eyes with plenty of water for at least 15 minutes. Get medical attention immediately.
Skin Contact	No emergency procedures necessary for intact tablets. If exposure occurs to crushed tablets, wash with soap and water. Remove contaminated clothing and shoes. Wash clothing before reuse. Thoroughly clean shoes before reuse. Get medical attention.
Inhalation	No emergency procedures necessary for intact tablets. If overexposure to dust from crushed tablets occurs, remove to fresh air. If breathing is difficult, give oxygen. If not breathing, give artificial respiration. Get medical attention if symptoms occur.
Ingestion	Compound not likely to create significant adverse effects at levels of exposure below 800 mg. Physician decision to treat is dependent on amount ingested.
Notes to physician	For additional guidance refer to the current prescribing information or the local poison control center.

5. Fire Fighting Measures

Flash Point	Not applicable
Flammable Limits (% in air)	Not applicable
Autoignition Temperature	Not relevant under normal conditions of product handling.
Oxidizing Properties	Not available
Combustibility Information	Not available
Dust Explosivity Information	Not available
Shock Sensitivity	Not available
Fire/Explosion Hazards	Not available
Special Fire Procedures	Fire fighters should wear positive pressure self-contained breathing apparatus (SCBA) and full turnout gear.
Extinguishing Media	In case of fire, use water spray (fog), foam or dry chemicals.
Hazardous Decomposition Products	These products are carbon oxides, nitrogen oxides, halogenated compounds, phosphates, hydrogen fluoride.

***** Continued on next page *****

Information Requested by Ms. Jessica Montealegre

6. Accidental Release Measures

Personal Precautions — Not necessary for small spills. For large spills, immediately contact emergency personnel. Keep unnecessary personnel away. Use suitable protective equipment (Section 8). Follow all fire fighting procedures (Section 5).

Methods for cleaning up — For small spill, tablets should be collected and disposed of as pharmaceutical waste. For large spill, if emergency personnel are unavailable, vacuum or carefully scoop up spilled materials and place in appropriate container for disposal. Avoid creating dusty conditions and prevent wind dispersal. Minimize contact of spilled material with soils to prevent runoff to surface waterways. **See Section 13 for Waste Disposal Information.**

For additional assistance in the U.S., CHEMTREC provides a toll-free Hotline for chemical emergencies regarding spills, leaks, exposure or accidents: 1-800-424-9300.
For emergency calls from outside the U.S.: 1-703-527-3887

7. Handling and Storage

Handling — No specific hazard with intact tablets. In case of exposure to crushed or broken tablets avoid contact with skin and eyes and wash thoroughly after handling.

Storage — Keep container tightly closed. Store up to 30º C (86º F).

8. Exposure Controls/Personal Protection

Exposure Guidelines

Component	OSHA Permissible Exposure Limit (PEL)	ACGIH Threshold Limit Value (TLV)	Merck Exposure Control Limit (ECL)
SITAGLIPTIN PHOSPHATE MONOHYDRATE	Not established	Not established	0.1 mg/m^3 (8-hr TWA)
Inactive Ingredients	- - -	- - -	- - -

ADI = 1 mg/day
Wipe Test Criteria - Not Required
PB-ECL Category 2 (Corresponds to 0.1-1 mg/m^2 as an 8-hr TWA)
PB-ECL catetory is an internal Merck control band.

Engineering Controls

Ventilation — None required with normal handling of finished product.

Personal Protective Equipment

Eye/Face Protection — None required with normal handling of finished product. Safety glasses recommended if potential exists for direct exposure to broken or crushed tablets or capsules.

Hand/Arm Protection — None required with normal handling of finished product. Impervious gloves recommended if the potential exists for direct exposure to broken or crushed tablets/capsules.

Respiratory Protection — None required with normal handling of finished product.

Additional Protective Equipment — No special recommendations.

***** Continued on next page *****

Information Requested by Ms. Jessica Montealegre

9. Physical and Chemical Properties

Appearance	25 mg - Pink round film coated tablet 50 mg - Light beige round film coated tablet 100 mg - Beige round film coated tablet
Odor/Threshold Limit	Not available
pH	Not available
Boiling Point	Not available
Melting Point	**SITAGLIPTIN PHOSPHATE MONOHYDRATE:** 216 to 222°C (420.8 to 431.6°F)
Flash point	Not applicable
Flammable Limits (% in air)	Not applicable
Autoignition Temperature	Not relevant under normal conditions of product handling.
Solubility	Not available
Partition Coefficient	Not available
Specific Gravity	Not applicable
Vapor Density	Not applicable
Vapor Pressure	Not applicable
Volatility Component	0% (w/w)

10. Stability and Reactivity

Stability	The product is stable.
Conditions to Avoid	**SITAGLIPTIN PHOSPHATE MONOHYDRATE:** No known chemical incompatibilities.
Incompatibility	None known under normal conditions of product handling.
Hazardous Polymerization	Will not occur.
Hazardous Decomposition Products	These products are carbon oxides, nitrogen oxides, halogenated compounds, phosphates, hydrogen fluoride.

11. Toxicological Information

Routes of Entry	Ingestion:	Intended route for clinical use.
	Inhalation:	Yes
	Skin Contact:	No.

Toxicity Data

Component	Test	Species	Route	Result
SITAGLIPTIN PHOSPHATE MONOHYDRATE	ALD50	Rat	Oral	>3000 mg/kg

Effects of Acute Exposure

Eye contact	None known under normal conditions of product handling. **SITAGLIPTIN PHOSPHATE MONOHYDRATE:** Moderately irritating to the eyes.

***** Continued on next page *****

Information Requested by Ms. Jessica Montealegre

Skin contact	None known under normal conditions of product handling. **SITAGLIPTIN PHOSPHATE MONOHYDRATE:** Not irritating to the skin. Not a skin sensitizer.
Inhalation	None expected with handling of finished product.
Ingestion	Intended route for clinical use.
Effects of Chronic Exposure	Finished product well tolerated in clinical use.

SITAGLIPTIN PHOSPHATE MONOHYDRATE: This compound is a dipeptidyl-peptidase IV (DP-IV) inhibitor used for the oral treatment of type 2 diabetes mellitus. In repeat-dose oral toxicity studies in dogs, physical signs (e.g., open mouth breathing, decreased activity, ataxia, tremors), emesis, dilation of lymphatic vessels in the eyelids, and very slight skeletal muscle degeneration were observed (LOAEL = 10 mg/kg/day). In repeat-dose studies in rats, incisor teeth, heart, liver and kidney changes were observed at dosages > 500 mg/kg/day. Kidney changes were observed in mice at 500 mg/kg/day. 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. 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 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.

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. Liver tumors were observed at 150 mg/kg. 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. 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. No adverse effect on fertility was observed at 125 mg/kg. At higher doses, nondose-related increased resorptions in females were observed.

The compound was well tolerated by healthy adults receiving single oral doses up to 800 mg/day with no serious adverse events reported. The most common adverse events reported in clinical studies of the compound (>/= 3% and more commonly in patients treated with placebo) were upper respiratory tract infection, nasopharyngitis, headache, diarrhea, arthalgia, and urinary tract infection.

Carcinogen Designation	Not listed as a carcinogen by OSHA, NTP or IARC.

***** Continued on next page *****

Information Requested by Ms. Jessica Montealegre

Medical Conditions Aggravated by Overexposure: Not available

12. Ecological Information

Environmental Effects: **SITAGLIPTIN PHOSPHATE MONOHYDRATE:** Harmful to aquatic organisms.

Ecotoxicity Data

Component	Species	Period	Result
SITAGLIPTIN PHOSPHATE MONOHYDRATE	*Daphnia magna* (EC50)	4 hours	60 mg/L
	Fathead minnow (LC50)	96 hours	>100 mg/L
	Algae (EC50)	72 hours	31 mg/L

Environmental Fate: **SITAGLIPTIN PHOSPHATE MONOHYDRATE:** No effect on sewage sludge respiration (ASRIT) at maximum concentration tested, 150 mg/L. Its Log Kow is -0.25, suggesting little potential for bioaccumulation. Sitgliptin is very stable and does not appreciably hydrolyze.

13. Disposal Considerations

Waste Disposal Information: Avoid contact of spilled material and runoff with soil and surface waterways. Dispose of or treat all spill residues including contaminated soils following all applicable regulations.

14. Transport Information

Shipping Description

U.S. DOT: Not regulated.

IATA/ICAO: Not regulated.

IMO: Not regulated.

ADR/RID: Not regulated.

15. Regulatory Information

U.S. Federal Regulations: Exempt from OSHA Hazard Communication Standard.

State Regulations: Not available

International Regulations: Exempt from the EU Dangerous Substances Directive.

16. Other Information

Date of Preparation: 1-May-2006

Date of Previous Issue: Not applicable

Validation Date: 12/8/2006.

***** Continued on next page *****

MSDS Coordinator:

1-908-423-7903
Merck & Co., Inc.
Two Merck Drive
P.O. Box 200, WS2W-13
Whitehouse Station, NJ 08889-0200
U.S.A.

Disclaimer:

While this information and recommendations set forth are believed to be accurate as of the date hereof, MERCK & CO, INC. makes no warranty with respect hereto and disclaims all liability from reliance thereon.

Information Requested by Ms. Jessica Montealegre

Information Requested by Ms. Jessica Montealegre

JANUVIA™
(sitagliptin) Tablets

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

- - - - - - - - - - - - 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 (PPARγ) 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 PPARγ 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	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 - - - - - - - - - - -
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 ≥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.

- - - - - - - - - - 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: 04/2007

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
- 1.1 Monotherapy
- 1.2 Combination Therapy
- 1.3 Important Limitations of Use

2 DOSAGE AND ADMINISTRATION
- 2.1 Recommended Dosing
- 2.2 Patients with Renal Insufficiency

3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS
- 7.1 Digoxin

8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES
- 14.1 Monotherapy
- 14.2 Combination Therapy

16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
- 17.1 Instructions
- 17.2 Laboratory Tests
- 17.3 FDA-Approved Patient Labeling

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Monotherapy
JANUVIA[1] 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 PPARγ 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 PPARγ agonist (e.g., thiazolidinediones). JANUVIA can be taken with or without food.

[1] Trademark of MERCK & CO., Inc., Whitehouse Station, New Jersey 08889 USA
COPYRIGHT © 2006, 2007 MERCK & CO., Inc. All rights reserved

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).]*

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 ≥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.

JANUVIA™ (sitagliptin) Tablets

Table 1
Placebo-Controlled Clinical Studies of JANUVIA Monotherapy or Combination with Pioglitazone: 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)

† 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 ≥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.

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, including anaphylaxis, angioedema, rash, and urticaria.

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.

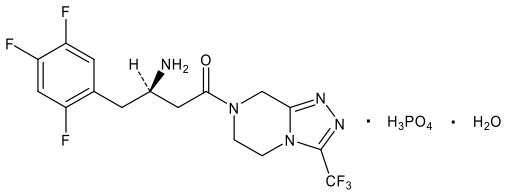
11 DESCRIPTION

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

Sitagliptin phosphate 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.

JANUVIA™ (sitagliptin) Tablets

The empirical formula is $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$ and the molecular weight is 523.32. The structural formula is:



Sitagliptin phosphate 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 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-fold 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 μM•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}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}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:

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

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 hemodialysis. *[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: Co-administration 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. However, the risk of hypoglycemia from the co-administration of sitagliptin and sulfonylureas is unknown.

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: Co-administration 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 co-administered medications:

Metformin: Co-administration 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. Co-administration 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 2316 patients with type 2 diabetes randomized in four double-blind, placebo-controlled clinical safety and efficacy studies conducted to evaluate the effects of sitagliptin on glycemic control. In these studies, the mean age of patients was 54.8 years, and 62% of patients were white, 18% were Hispanic, 6% were black, 9% were Asian, and 4% were of other racial groups.

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 wash-out period of about 7 weeks. Patients with inadequate glycemic control (A1C 7% to 10%) after the wash-out 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 2). 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 was not affected by gender, age, race, or baseline BMI. As is typical for trials of agents to treat type 2 diabetes, mean response to JANUVIA in A1C lowering appears to be related to the degree of A1C elevation at baseline. 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 2
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
A1C (%)	**N = 193**	**N = 103**	**N = 229**	**N = 244**
Baseline (mean)	8.0	8.1	8.0	8.0
Change from baseline (adjusted mean‡)	-0.5	0.1	-0.6	0.2
Difference from placebo (adjusted mean‡) (95% CI)	-0.6§ (-0.8, -0.4)		-0.8§ (-1.0, -0.6)	
Patients (%) achieving A1C <7%	69 (36%)	16 (16%)	93 (41%)	41 (17%)
FPG (mg/dL)	**N = 201**	**N = 107**	**N = 234**	**N = 247**
Baseline (mean)	180	184	170	176
Change from baseline (adjusted mean‡)	-13	7	-12	5
Difference from placebo (adjusted mean‡) (95% CI)	-20§ (-31, -9)		-17§ (-24, -10)	
2-hour PPG (mg/dL)	‖	‖	**N = 201**	**N = 204**
Baseline (mean)			257	271
Change from baseline (adjusted mean‡)			-49	-2
Difference from placebo (adjusted mean‡) (95% CI)			-47§ (-59, -34)	

† Intent to Treat Population using last observation on study prior to metformin rescue therapy.

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

§ p<0.001 compared to placebo.

‖ 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

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 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 3). 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.

JANUVIA™ (sitagliptin) Tablets

Table 3
Glycemic Parameters at Final Visit (24-Week Study) for JANUVIA in Combination with Metformin†

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

† Intent to Treat Population using last observation on study prior to pioglitazone rescue therapy.

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

§ p<0.001 compared to placebo + metformin.

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 PPARγ 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 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 included A1C and fasting glucose.

In combination with pioglitazone, JANUVIA provided significant improvements in A1C and FPG compared to placebo with pioglitazone (Table 4). 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 4
Glycemic Parameters at Final Visit (24-Week Study) for JANUVIA in Combination with Pioglitazone†

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

† Intent to Treat Population using last observation on study prior to metformin rescue therapy.

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

§ p<0.001 compared to placebo + pioglitazone.

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 0006-0277-28 unit dose blister packages of 100

NDC 0006-0277-74 bottles of 500

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 (17.3).]

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.

Physicians should instruct their patients to read the Patient Package Insert 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.

Manufactured for:

MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Manufactured by:

Merck Sharp & Dohme (Italia) S.p.A.
Via Emilia, 21
27100 – Pavia, Italy

Printed in USA

9762702

US Patent No.: 6,699,871

17.3 FDA-Approved Patient Labeling

Patient Information
JANUVIA™ (jah-NEW-vee-ah)
(sitagliptin)

Tablets

Read the Patient Information that comes with JANUVIA* before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or treatment.

What is JANUVIA?

JANUVIA is a prescription medicine used along with diet and exercise to lower blood sugar in patients with type 2 diabetes mellitus (type 2 diabetes). JANUVIA may be taken alone or along with certain other medicines to control blood sugar.

- JANUVIA lowers blood sugar when blood sugar is high, especially after a meal. JANUVIA also lowers blood sugar between meals.
- JANUVIA helps to improve the levels of insulin produced by your own body after a meal.
- JANUVIA decreases the amount of sugar made by the body. JANUVIA is unlikely to cause your blood sugar to be lowered to a dangerous level (hypoglycemia) because it does not work when your blood sugar is low.

JANUVIA has not been studied in children under 18 years of age.

JANUVIA has not been studied with medicines known to cause low blood sugar, such as sulfonylureas or insulin. Ask your doctor if you are taking a sulfonylurea or other medicine that can cause low blood sugar.

Who should not take JANUVIA?

JANUVIA should not be used to treat patients with:

- Type 1 diabetes mellitus
- Diabetic ketoacidosis (increased ketones in the blood or urine).

What should I tell my doctor before and during treatment with JANUVIA?

Tell your doctor about all of your medical conditions, including if you:

- have any allergies
- have kidney problems
- are pregnant or plan to become pregnant, because JANUVIA may not be right for you. 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. If you use JANUVIA during pregnancy, talk with your doctor about how you can be on the JANUVIA registry. The toll-free telephone number for the pregnancy registry is: 1-800-986-8999.
- are breast-feeding or plan to breast-feed. JANUVIA may be passed in your milk to your baby. 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 non-prescription 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.

During periods of stress on the body, such as fever, trauma, infection or surgery, your medication needs may change; contact your doctor right away.

How should I take JANUVIA?

- Take JANUVIA exactly as your doctor tells you to take it.
- Take JANUVIA by mouth once a day.
- Take JANUVIA with or without food.
- If you have kidney problems, your doctor may prescribe lower doses of JANUVIA. Your doctor may perform blood tests on you from time to time to measure how well your kidneys are working.
- Your doctor may prescribe JANUVIA along with certain other medicines that lower blood sugar.

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 a double dose of JANUVIA.

If you take too much JANUVIA, call your doctor or local Poison Control Center right away.

*Trademark of MERCK & CO., Inc., Whitehouse Station, New Jersey, 08889 USA
COPYRIGHT © 2006, 2007 MERCK & CO., Inc.
All rights reserved

What else should I know about blood sugar control?

- Monitor 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 complications of diabetes.
- Your doctor will monitor your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1C.

What are the possible side effects of JANUVIA?

The most common side effects of JANUVIA include:

- Upper respiratory infection
- Stuffy or runny nose and sore throat
- Headache

JANUVIA may occasionally cause stomach discomfort and diarrhea.

The following additional side effects have been reported in general use with JANUVIA:

- Allergic reactions (which may require treatment right away) including swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing, rash, and hives.

Tell your doctor if you have any side effect that bothers you or that does not go away. Other side effects may occur when using JANUVIA. For more information, ask your doctor or pharmacist.

How should I store JANUVIA?

- Store JANUVIA at room temperature, 68 to 77°F (20 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 conditions that are not mentioned in patient information leaflets. 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 leaflet 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 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.

The main goal of treating diabetes is to lower your blood sugar to a normal level. Lowering and controlling blood sugar may help prevent or delay complications of diabetes, such as heart disease, kidney disease, blindness, and amputation.

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

Issued April 2007

Manufactured for:

MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Manufactured by:

Merck Sharp & Dohme (Italia) S.p.A.
Via Emilia, 21
27100 – Pavia, Italy

9762702