CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 021995/S-014

Trade Name: **JANUVIA**

Generic Name: **Sitagliptin**

Sponsor: **Merck & Co., Inc.**

Approval Date: 02/26/2010

Indications: 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.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021995/S-014

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	**X**
Labeling	**X**
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	**X**
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	**X**
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Risk Assessment and Risk Mitigation Review(s)	**X**
Proprietary Name Review(s)	
Other Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021995/S-014

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021995/S-010, S-011, S-012 and S-014 **SUPPLEMENT APPROVAL**

Merck Sharp and Dohme Corp.
Attention: Richard J. Swanson, Ph.D.
Director, Regulatory Affairs
P.O. Box 1000, UG2C-50
North Wales, PA 19454-1099

Dear Dr. Swanson:

Please refer to your supplemental new drug applications (sNDAs) dated and received December 18, 2008 (S-010), December 19, 2008 (S-011), February 23, 2009 (S-012) and November 13, 2009 (S-014), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Januvia (sitagliptin) tablets.

We also acknowledge receipt of your submissions dated February 17, 2010 (S-010 and S-011), January 6 and 20, and February 17, 2010 (S-012) and December 21 and 31, 2009, and January 5, 15, 20 and 21, and February 4, 8, 19 and 23, 2010 (S-014).

Your submissions of February 17, 2010 (S-010 and S-011), and January 20, 2010 (S-012), constitute a complete response to our January 25, 2010 and December 21, 2009 action letters, respectively.

The "Prior Approval" supplemental applications S-010, S-011 and S-012 provide for the use of Januvia (sitagliptin) in combination with metformin and a PPARγ agonist as an adjunct to diet and exercise in adult patients with type 2 diabetes mellitus who are inadequately controlled on combination therapy with metformin and a PPARγ agonist (S-010), for the use of Januvia (sitagliptin) as combination therapy with a PPARγ agonist (S-011), and for the use of Januvia in combination with insulin, alone or in combination with metformin (S-012). The "Prior Approval" supplement S-014 contains proposed safety related labeling changes to the Package Insert regarding the risk of pancreatitis as well as a newly created Medication Guide, and a proposed Risk Evaluation and Mitigation Strategy (REMS). The Package Insert containing the pancreatitis-related changes was approved under supplemental application S-013 on December 28, 2009.

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert and the Medication Guide). For administrative purposes, please designate this submission, "SPL for approved NDA 021995/S-010, S-011, S-012 and S-014".

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed representative carton and immediate container labels submitted on February 23, 2010, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "Final Printed Carton and Container Labels for approved NDA 021995/S-014". Approval of this submission by FDA is not required before the labeling is used.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

Since Januvia (sitagliptin) was approved on October 16, 2006, we have become aware of 88 cases of pancreatitis associated with the use of sitagliptin in FDA's Adverse Event Reporting System (AERS) database. These include two cases of necrotizing pancreatitis. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

Your proposed REMS, submitted on November 13, 2009, amended on January 5, 15 and 20, and February 4, 8 and 19, 2010, and appended to this letter, is approved. The REMS consists of the Medication Guide included with this letter and the timetable for submission of assessments of the REMS.

Your assessment of the REMS should include an evaluation of patients' understanding of the serious risks of Januvia (sitagliptin).

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), requirements for information on the status of any postapproval

study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify submissions containing REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission:

NDA 021995 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 021995
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT FOR (NEW INDICATION FOR USE)
FOR NDA 021995
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

Since Januvia (sitagliptin) was approved on October 16, 2006, we have become aware of "new safety information" as described above.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of acute pancreatitis, including necrotizing forms, associated with the use of Januvia (sitagliptin).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

> **1602**: A 3-month pancreatic safety study in a diabetic rodent model treated with sitagliptin.

The timetable you submitted on January 21, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	June 15, 2010
Study Completion Date:	March 15, 2011
Final Report Submission:	June 15, 2011

Submit the protocol to your IND, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in

this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the following address or by facsimile at 301-847-8444:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

In addition, as required under 21 CFR 314.81(b)(3)(i), you must submit your updated final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA-2253, directly to the above address. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Mehreen Hai, Ph.D., Regulatory Project Manager, at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
- Package Insert
- Medication Guide
- REMS
- Carton and Container Labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21995	SUPPL-12	MERCK CO INC	JANUVIA 100MG (SITAGLIPTIN PHOSPHATE)
NDA-21995	SUPPL-14	MERCK CO INC	JANUVIA 100MG (SITAGLIPTIN PHOSPHATE)
NDA-21995	SUPPL-11	MERCK CO INC	JANUVIA 100MG (SITAGLIPTIN PHOSPHATE)
NDA-21995	SUPPL-10	MERCK CO INC	JANUVIA 100MG (SITAGLIPTIN PHOSPHATE)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY H PARKS
02/26/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021995/S-014

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) Tablets
Initial U.S. Approval: 2006

---------- RECENT MAJOR CHANGES ----------

Indications and Usage	
Important Limitations of Use (1.2)	12/2009
Dosage and Administration	
Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin (2.3)	XX/20XX
Warnings and Precautions	
Pancreatitis (5.1)	12/2009
Use with Medications Known to Cause Hypoglycemia (5.3)	XX/20XX

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

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

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

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

Dosage Adjustment in Patients With Moderate, Severe and End Stage Renal Disease (ESRD) (2.2)	
50 mg once daily	25 mg once daily
Moderate 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 (5.4, 6.2)

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

---------- 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. In the add-on to sulfonylurea and add-on to insulin studies, hypoglycemia was also more commonly reported in patients treated with JANUVIA compared to placebo. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- 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 Medication Guide.

Revised: XX/20XX

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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 patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using JANUVIA. *[See Warnings and Precautions (5.1).]*

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

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

2.2 Patients with Renal Insufficiency

For patients with mild renal insufficiency (creatinine clearance [CrCl] ≥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 an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Pancreatitis

There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking JANUVIA. After initiation of JANUVIA, patients

should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, JANUVIA should promptly be discontinued and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using JANUVIA.

5.2 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).]*

5.3 Use with Medications Known to Cause Hypoglycemia

When JANUVIA was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin. *[See Adverse Reactions (6.1).]* Therefore, a lower dose of sulfonylurea or insulin may be required to reduce the risk of hypoglycemia. *[See Dosage and Administration (2.3).]*

5.4 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with JANUVIA. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. 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).]*

5.5 Macrovascular Outcomes

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

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

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

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

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

† Intent to treat population

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

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

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

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

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

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

	Number of Patients (%)			
	Placebo	**Sitagliptin (JANUVIA) 100 mg QD**	**Metformin 500 or 1000 mg bid ††**	**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.

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

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

Hypoglycemia

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

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

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

† Adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia; a concurrent glucose measurement was not required; intent to treat population.
‡ Based on total number of events (i.e., a single patient may have had multiple events).
§ Severe events of hypoglycemia were defined as those events requiring medical assistance or exh biting depressed level/loss of consciousness or seizure.

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

In the study of JANUVIA as add-on combination therapy with metformin and rosiglitazone, the overall incidence of hypoglycemia was 2.2% in patients given add-on JANUVIA and 0.0% in patients given add-

on placebo through Week 18. Through Week 54, the overall incidence of hypoglycemia was 3.9% in patients given add-on JANUVIA and 1.0% in patients given add-on placebo.

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

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

Laboratory Tests

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

6.2 Postmarketing Experience

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, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome *[see Warnings and Precautions (5.4)]*; hepatic enzyme elevations; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis *[see Limitations of Use (1.2); Warnings and Precautions (5.1)]*.

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

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

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

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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

10 OVERDOSAGE

During controlled clinical trials in healthy subjects, single doses of up to 800 mg JANUVIA were administered. Maximal mean increases in QTc of 8.0 msec were observed in one study at a dose of 800 mg JANUVIA, a mean effect that is not considered clinically important *[see Clinical Pharmacology (12.2)]*. There is no experience with doses above 800 mg in humans. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with JANUVIA with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for up to 28 days.

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

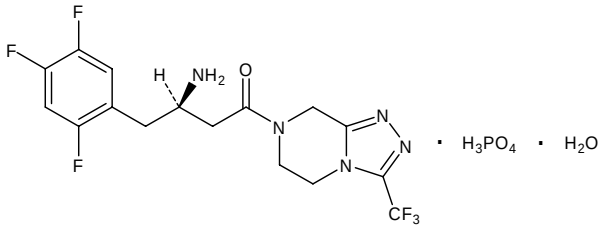
Sitagliptin is modestly dialyzable. In clinical studies, approximately 13.5% of the dose was removed over a 3- to 4-hour hemodialysis session. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialyzable by peritoneal dialysis.

11 DESCRIPTION

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

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

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



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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

General

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

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

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

Cardiac Electrophysiology

In a randomized, placebo-controlled crossover study, 79 healthy subjects were administered a single oral dose of JANUVIA 100 mg, JANUVIA 800 mg (8 times the recommended dose), and placebo. At the recommended dose of 100 mg, there was no effect on the QTc interval obtained at the peak plasma concentration, or at any other time during the study. Following the 800 mg dose, the maximum increase

in the placebo-corrected mean change in QTc from baseline was observed at 3 hours postdose and was 8.0 msec. This increase is not considered to be clinically significant. At the 800 mg dose, peak sitagliptin plasma concentrations were approximately 11 times higher than the peak concentrations following a 100 mg dose.

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

12.3 Pharmacokinetics

The pharmacokinetics of sitagliptin has been extensively characterized in healthy subjects and patients with type 2 diabetes. After oral administration of a 100 mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1 to 4 hours postdose. Plasma AUC of sitagliptin increased in a dose-proportional manner. Following a single oral 100 mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8.52 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.

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 approximately 5200 patients with type 2 diabetes randomized in nine double-blind, placebo-controlled clinical safety and efficacy studies conducted to evaluate the effects of sitagliptin on glycemic control. In a pooled analysis of seven of these studies, the ethnic/racial distribution was approximately 59% white, 20% Hispanic, 10% Asian, 6% black, and 6% other groups. Patients had an overall mean age of approximately 55 years (range 18 to 87 years). In addition, an active (glipizide)-controlled study of 52-weeks duration was conducted in 1172 patients with type 2 diabetes who had inadequate glycemic control on metformin.

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

14.1 Monotherapy

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

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

Table 4
Glycemic Parameters in 18- and 24-Week Placebo-Controlled Studies of JANUVIA in Patients with Type 2 Diabetes[†]

	18-Week Study		24-Week Study	
	JANUVIA 100 mg	**Placebo**	**JANUVIA 100 mg**	**Placebo**
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

Add-on Combination Therapy with Metformin

A total of 701 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of JANUVIA in combination with metformin. Patients already on metformin (N=431) at a dose of at least 1500 mg per day were randomized after completing a 2-week single-blind placebo run-in period. Patients on metformin and another antihyperglycemic agent (N=229) and patients not on any antihyperglycemic agents (off therapy for at least 8 weeks, N=41) were randomized after a run-in period of approximately 10 weeks on metformin (at a dose of at least 1500 mg per day) in monotherapy. Patients with inadequate glycemic control (A1C 7% to 10%) were randomized to the addition of either 100 mg of JANUVIA or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with pioglitazone rescue.

In combination with metformin, JANUVIA provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo with metformin (Table 5). Rescue glycemic therapy was used in 5% of patients

treated with JANUVIA 100 mg and 14% of patients treated with placebo. A similar decrease in body weight was observed for both treatment groups.

Table 5
Glycemic Parameters at Final Visit (24-Week Study)
for JANUVIA in Add-on Combination Therapy with Metformin[†]

	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.

Initial Combination Therapy with Metformin

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

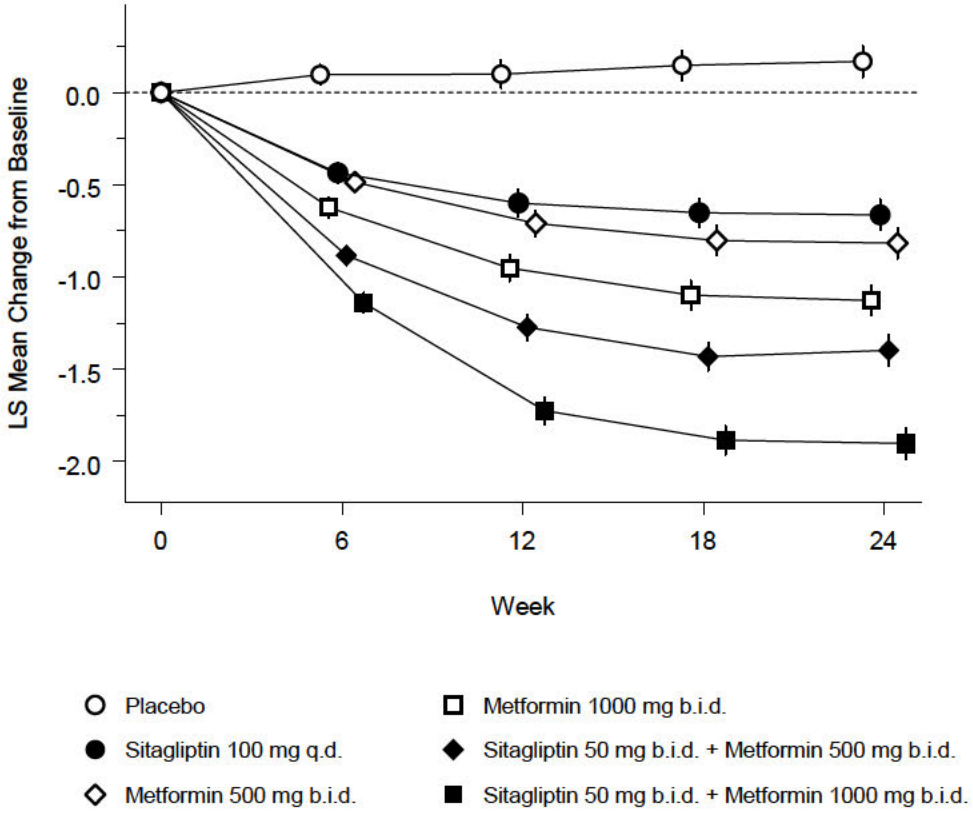
Initial therapy with the combination of JANUVIA and metformin provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo, to metformin alone, and to JANUVIA alone (Table 6, Figure 1). Mean reductions from baseline in A1C were generally greater for patients with higher baseline A1C values. For patients not on an antihyperglycemic agent at study entry, mean reductions from baseline in A1C were: JANUVIA 100 mg once daily, -1.1%; metformin 500 mg bid, -1.1%; metformin 1000 mg bid, -1.2%; sitagliptin 50 mg bid with metformin 500 mg bid, -1.6%; sitagliptin 50 mg bid with metformin 1000 mg bid, -1.9%; and for patients receiving placebo, -0.2%. Lipid effects were generally neutral. The decrease in body weight in the groups given sitagliptin in combination with metformin was similar to that in the groups given metformin alone or placebo.

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

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

[†] Intent to Treat Population using last observation on study prior to glyburide (glibenclamide) rescue therapy.
[‡] Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
[§] p<0.001 compared to placebo.

Figure 1: Mean Change from Baseline for A1C (%) over 24 Weeks with Sitagliptin and Metformin, Alone and in Combination as Initial Therapy in Patients with Type 2 Diabetes†



†All Patients Treated Population Least squares means adjusted for prior antihyperglycemic therapy and baseline value.

In addition, this study included patients (N=117) with more severe hyperglycemia (A1C >11% or blood glucose >280 mg/dL) who were treated with twice daily open-label JANUVIA 50 mg and metformin 1000 mg. In this group of patients, the mean baseline A1C value was 11.2%, mean FPG was 314 mg/dL, and mean 2-hour PPG was 441 mg/dL. After 24 weeks, mean decreases from baseline of -2.9% for A1C, -127 mg/dL for FPG, and -208 mg/dL for 2-hour PPG were observed.

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

Active-Controlled Study vs Glipizide in Combination with Metformin

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

After 52 weeks, JANUVIA and glipizide had similar mean reductions from baseline in A1C in the intent-to-treat analysis (Table 7). These results were consistent with the per protocol analysis (Figure 2).

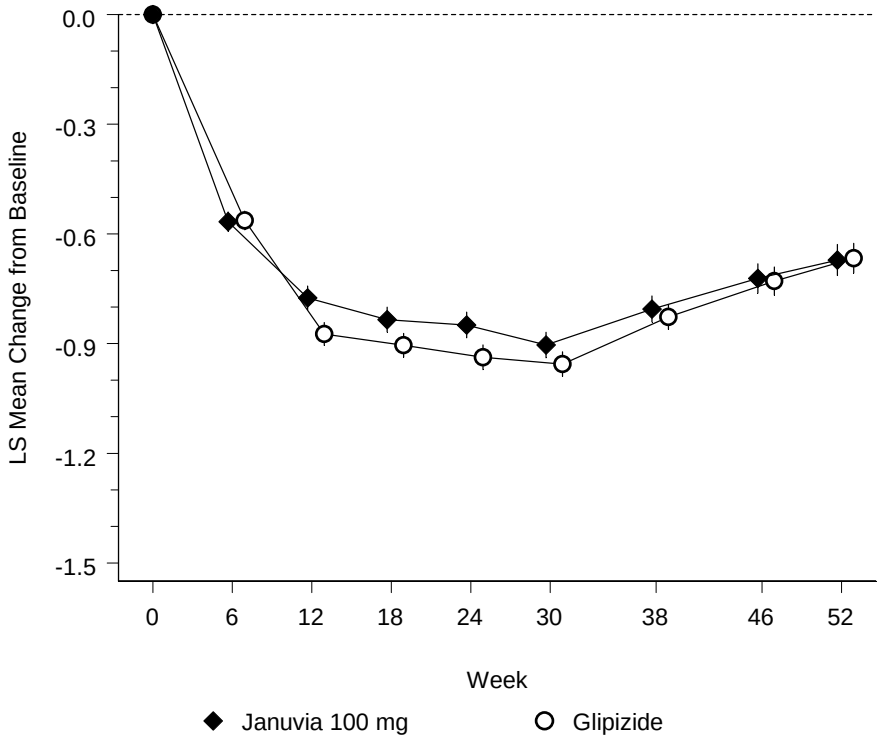
A conclusion in favor of the non-inferiority of JANUVIA to glipizide may be limited to patients with baseline A1C comparable to those included in the study (over 70% of patients had baseline A1C <8% and over 90% had A1C <9%).

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

	JANUVIA 100 mg	Glipizide
A1C (%)	**N = 576**	**N = 559**
Baseline (mean)	7.7	7.6
Change from baseline (adjusted mean‡)	-0.5	-0.6
FPG (mg/dL)	**N = 583**	**N = 568**
Baseline (mean)	166	164
Change from baseline (adjusted mean‡)	-8	-8

† The Intent to Treat Analysis used the patients' last observation in the study prior to discontinuation.
‡ Least squares means adjusted for prior antihyperglycemic therapy status and baseline A1C value.

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



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

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

Add-on Combination Therapy with Pioglitazone

A total of 353 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of JANUVIA in combination with pioglitazone. Patients on any oral antihyperglycemic agent in monotherapy (N=212) or on a 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 with inadequate glycemic control (A1C 7% to 10%) were randomized to the addition of either 100 mg of JANUVIA or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with metformin rescue. Glycemic endpoints measured were A1C and fasting glucose.

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

Table 8
Glycemic Parameters at Final Visit (24-Week Study)
for JANUVIA in Add-on Combination Therapy with Pioglitazone[†]

	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.

Initial Combination Therapy with Pioglitazone

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

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

Table 9
Glycemic Parameters at Final Visit (24-Week Study)
for JANUVIA in Combination with Pioglitazone as Initial Therapy[†]

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

[†] Intent to Treat Population using last observation on study.
[‡] Least squares means adjusted for baseline value.
[§] p<0.001 compared to placebo + pioglitazone.

Add-on Combination Therapy with Metformin and Rosiglitazone

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

In combination with metformin and rosiglitazone, JANUVIA provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo with metformin and rosiglitazone (Table 10) at Week 18. At Week 54, mean reduction in A1C was -1.0% for patients treated with JANUVIA and -0.3% for patients treated with placebo in an analysis based on the intent to treat population. Rescue therapy was used in 18% of patients treated with JANUVIA 100 mg and 40% of patients treated with placebo. There was no significant difference between JANUVIA and placebo in body weight change.

Table 10
Glycemic Parameters at Week 18
for JANUVIA in Add-on Combination Therapy with Metformin and Rosiglitazone[†]

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

[†] Intent to Treat Population using last observation on study prior to glipizide (or other sulfonylurea) rescue therapy.
[‡] Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
[§] p<0.001 compared to placebo + metformin + rosiglitazone.

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

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

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

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

	JANUVIA 100 mg + Glimepiride	Placebo + Glimepiride	JANUVIA 100 mg + Glimepiride + Metformin	Placebo + Glimepiride + Metformin
A1C (%)	**N = 102**	**N = 103**	**N = 115**	**N = 105**
Baseline (mean)	8.4	8.5	8.3	8.3
Change from baseline (adjusted mean[‡])	-0.3	0.3	-0.6	0.3
Difference from placebo (adjusted mean[‡]) (95% CI)	-0.6[§] (-0.8, -0.3)		-0.9[§] (-1.1, -0.7)	
Patients (%) achieving A1C <7%	11 (11%)	9 (9%)	26 (23%)	1 (1%)
FPG (mg/dL)	**N = 104**	**N = 104**	**N = 115**	**N = 109**
Baseline (mean)	183	185	179	179
Change from baseline (adjusted mean[‡])	-1	18	-8	13
Difference from placebo (adjusted mean[‡]) (95% CI)	-19[‖] (-32, -7)		-21[§] (-32, -10)	

[†] Intent to Treat Population using last observation on study prior to pioglitazone rescue therapy.
[‡] Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
[§] p<0.001 compared to placebo.
[‖] p<0.01 compared to placebo.

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

A total of 641 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of JANUVIA as add-on to insulin therapy (with or without metformin). The racial distribution in this study was approximately 70% white, 18% Asian, 7% black, and 5% other groups. Approximately 14% of the patients in this study were Hispanic. Patients entered a 2-week, single-blind run-in treatment period on pre-mixed, long-acting, or intermediate-acting insulin, with or without metformin (≥1500 mg per day). Patients using short-acting insulins were excluded unless the short-acting insulin was administered as part of a pre-mixed insulin. After the run-in period, patients with inadequate glycemic control (A1C 7.5% to 11%) were randomized to the addition of either 100 mg of JANUVIA or placebo, administered once daily. Patients were on a stable dose of insulin prior to enrollment with no changes in insulin dose permitted during the run-in period. Patients who failed to meet specific glycemic goals during the double-blind treatment period were to have uptitration of the background insulin dose as rescue therapy.

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

Table 12
Glycemic Parameters at Final Visit (24-Week Study)
for JANUVIA as Add-on Combination Therapy with Insulin[†]

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

[†] Intent to Treat Population using last observation on study prior to rescue therapy.
[‡] Least squares means adjusted for metformin use at the screening visit (yes/no), type of insulin used at the screening visit (pre-mixed vs. non-pre-mixed [intermediate- or long-acting]), and baseline value.
[§] Treatment by stratum interaction was not significant (p>0.10) for metformin stratum and for insulin stratum.
[‖] p<0.001 compared to placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

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

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

NDC 0006-0277-31 unit-of-use bottles of 30
NDC 0006-0277-54 unit-of-use bottles of 90
NDC 0006-0277-28 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 Medication Guide.

17.1 Instructions

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

Patients should be informed that acute pancreatitis has been reported during postmarketing use of JANUVIA. Patients should be informed that persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Patients should be instructed to promptly discontinue JANUVIA and contact their physician if persistent severe abdominal pain occurs *[see Warnings and Precautions (5.1)].*

Patients should be informed that the incidence of hypoglycemia is increased when JANUVIA is added to a sulfonylurea or insulin and that a lower dose of the sulfonylurea or insulin may be required to reduce the risk of hypoglycemia.

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

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

17.2 Laboratory Tests

Patients should be informed that response to all diabetic therapies should be monitored by periodic measurements of blood glucose and A1C levels, with a goal of decreasing these levels towards the normal range. A1C is especially useful for evaluating long-term glycemic control. Patients should be informed of the potential need to adjust dose based on changes in renal function tests over time.

Manuf. for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Manufactured by:

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

XXXXXXX

US Patent No.: 6,699,871

[1] Registered trademark of Merck Sharp & Dohme Corp., a subsidiary of **Merck & Co., Inc.**

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

Tablets

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

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

Serious side effects can happen in people taking JANUVIA, including inflammation of the pancreas (pancreatitis) which may be severe and lead to death.

Certain medical problems make you more likely to get pancreatitis.

Before you start taking JANUVIA:
Tell your doctor if you have ever had

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

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

What is JANUVIA?

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

Who should not take JANUVIA?

Do not take JANUVIA if:

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

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

What should I tell my doctor before taking JANUVIA?

Before you take JANUVIA, tell your doctor if you:

- have or have had inflammation of your pancreas (pancreatitis).
- have kidney problems.
- have any other medical conditions.
- are pregnant or plan to become pregnant. It is not known if JANUVIA will harm your unborn baby. If you are pregnant, talk with your doctor about the best way to control your blood sugar while you are pregnant.
  Pregnancy Registry: If you take JANUVIA at any time during your pregnancy, talk with your doctor about how you can join the JANUVIA pregnancy registry. The purpose of this registry is to collect information about the health of you and your baby. You can enroll in this registry by calling 1-800-986-8999.
- are breast-feeding or plan to breast-feed. It is not known if JANUVIA will pass into your breast milk. Talk with your doctor about the best way to feed your baby if you are taking JANUVIA.

Tell your doctor about all the medicines you take, including prescription and 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.

How should I take JANUVIA?

- Take JANUVIA 1 time each day exactly as your doctor tells you.
- You can take JANUVIA with or without food.
- Your doctor may do blood tests from time to time to see how well your kidneys are working. Your doctor may change your dose of JANUVIA based on the results of your blood tests.
- Your doctor may tell you to take JANUVIA along with other diabetes medicines. Low blood sugar can happen more often when JANUVIA is taken with certain other diabetes medicines. See "**What are the possible side effects of JANUVIA?**"
- If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take two doses of JANUVIA at the same time.
- If you take too much JANUVIA, call your doctor or local Poison Control Center right away.
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection or surgery, the amount of diabetes medicine that you need may change. Tell your doctor right away if you have any of these conditions and follow your doctor's instructions.
- Check your blood sugar as your doctor tells you to.
- Stay on your prescribed diet and exercise program while taking JANUVIA.
- Talk to your doctor about how to prevent, recognize and manage low blood sugar (hypoglycemia), high blood sugar (hyperglycemia), and problems you have because of your diabetes.
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1C.

What are the possible side effects of JANUVIA?

Serious side effects have occurred in people taking JANUVIA.

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

- **Low blood sugar (hypoglycemia).** If you take JANUVIA with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you use JANUVIA. Signs and symptoms of low blood sugar may include:

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

- **Serious allergic reactions.** If you have any symptoms of a serious allergic reaction, stop taking JANUVIA and call your doctor right away. See "**Who should not take JANUVIA?**". Your doctor may give you a medicine for your allergic reaction and prescribe a different medicine for your diabetes.

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

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

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

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

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

How should I store JANUVIA?
Store JANUVIA at 68°F to 77°F (20°C to 25°C).

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

General information about the use of JANUVIA
Medicines are sometimes prescribed for purposes that are not listed in Medication Guides. Do not use JANUVIA for a condition for which it was not prescribed. Do not give JANUVIA to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about JANUVIA. If you would like to know more information, talk with your doctor. You can ask your doctor or pharmacist for additional information about JANUVIA that is written for health professionals. For more information, go to www.JANUVIA.com or call 1-800-622-4477.

What are the ingredients in JANUVIA?
Active ingredient: sitagliptin

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

What is type 2 diabetes?

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

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

Revised Month Year

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

XXXXXXX

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021995/S-014

REMS

NDA 21-995

JANUVIA

(sitagliptin)

Tablet

Dipeptidyl peptidase 4 (DPP-4) inhibitor

Merck Sharp & Dohme Corp.

One Merck Drive

P.O. Box 100

Whitehouse Station, NJ 08889-0100

(908) 423-1000

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S)

The goal of this REMS is to inform the patients of the serious risks associated with the use of JANUVIA (sitagliptin).

II. REMS ELEMENTS

A. Medication Guide

Merck Sharp & Dohme Corp. ("Merck") in accordance with 21 CFR 208.24(b) will ensure that the currently approved Medication Guide is available for distribution to patients and dispensed with each JANUVIA prescription.

Merck in accordance with 21 CFR 208.24 will provide the currently approved Medication Guide in sufficient numbers for distribution. Merck will attach a JANUVIA (sitagliptin) Medication Guide to each unit-of-use package of JANUVIA (sitagliptin) to ensure that the Medication Guide is given to each patient with each new prescription and refill. In addition, copies of the Medication Guide may also be provided to US pharmacies for direct distribution to patients.

In accordance with 21 CFR 208.24(d), the JANUVIA (sitagliptin) container labels will include an instruction to the authorized dispenser to provide a copy of the Medication Guide to each patient to whom JANUVIA (sitagliptin) is dispensed.

The Medication Guide will also be available on JANUVIA's website at www.Januvia.com.

B. Timetable for Submission of Assessments

Merck will submit REMS Assessment to FDA 18 months, 3 years, and 7 years from the date of the approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment.

Merck will submit each assessment so that it will be received by the FDA on or before the due date.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21995	SUPPL-12	MERCK CO INC	JANUVIA 100MG (SITAGLIPTIN PHOSPHATE)
NDA-21995	SUPPL-14	MERCK CO INC	JANUVIA 100MG (SITAGLIPTIN PHOSPHATE)
NDA-21995	SUPPL-11	MERCK CO INC	JANUVIA 100MG (SITAGLIPTIN PHOSPHATE)
NDA-21995	SUPPL-10	MERCK CO INC	JANUVIA 100MG (SITAGLIPTIN PHOSPHATE)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY H PARKS
02/26/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021995/S-014

OTHER REVIEW(S)

Division of Metabolism and Endocrinology Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 21-995/S-010, S-011, S-012 and S-014

Name of Drug: Januvia (sitagliptin) Tablets

Applicant: Merck Sharp & Dohme Corp.

Material Reviewed:

Submission Date	Receipt Date	Document Type
February 17, 2010	February 17, 2010	Package Insert (PI)
February 23, 2010	February 23, 2010	Draft Carton and Container Labeling

Background and Summary

NDA 21-995 for Januvia (sitagliptin) Tablets was approved on October 16, 2006, as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus as monotherapy and in combination with metformin or a PPARγ agonist (e.g., thiazolidinediones) when diet and exercise plus the single agent do not provide adequate glycemic control.

The currently approved Package Insert was submitted on December 3, 2009, and approved on December 28, 2009, for Supplement-013.

The "Prior Approval" supplements S-010, S-011 and S-012 provide for the use of Januvia (sitagliptin) in combination with metformin and a PPARγ agonist as an adjunct to diet and exercise in adult patients with type 2 diabetes mellitus who are inadequately controlled on combination therapy with metformin and a PPARγ agonist (S-010, submitted December 18, 2008), for the use of Januvia (sitagliptin) as combination therapy with a PPARγ agonist (S-011, submitted December 19, 2008), and for the use of Januvia in combination with insulin, alone or in combination with metformin (S-012, submitted February 23, 2009). Complete response letters were issued for all three supplements, since agreement had not been reached regarding the language and placement of the information regarding the risk of pancreatitis under S-013 (see info regarding S-013 below). S-010 and S-011 were re-submitted on November 25, 2009, issued complete response letters again for the same reason as above, and re-submitted again on February 17, 2010. S-012 was re-submitted on January 20, 2010. The Package Insert containing the agreed-upon changes proposed for all three supplements was submitted on February 17, 2010.

On March 5, 2009, Merck submitted a "Changes Being Effected" supplemental new drug application (S-013) that provided for the addition of "cutaneous vasculitis" and "pancreatitis" to

the Postmarketing Experience subsection of the Adverse Reactions section of the package insert (PI), and proposed the addition of "inflammation of the pancreas" to the patient package insert. Subsequently, FDA became aware of 88 cases of pancreatitis associated with the use of sitagliptin in FDA's Adverse Event Reporting System (AERS) database. These include two cases of necrotizing pancreatitis. This information was considered to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

Based on this information, FDA recommended that Merck move the information regarding pancreatitis to the 'Important Limitations of Use' and the 'Warnings and Precautions' subsections of the Highlights of Prescribing Information section, as well as to the corresponding sub-sections of the 'Full Prescribing Information' section of the PI for Januvia. FDA and Merck were unable to reach agreement regarding the extent and placement of the information about pancreatitis in the PI. On October 16, 2009, FDA issued a Complete Response (CR) letter for supplement S-013, describing required safety labeling changes, as authorized by Sections 505(o)(4) and 505-1 of the FDCA, regarding the placement of the pancreatitis information in the PI. The CR letter also required Merck to develop and comply with a Risk Evaluation and Mitigation Strategies (REMS) containing a Medication Guide and a Timetable for Submission of Assessments, and to conduct a 3-month pancreatic safety study in a diabetic rodent model treated with sitagliptin as a post-marketing requirement (PMR).

On November 13, 2009, Merck submitted supplement S-014, containing all of the required items described above. The November 13, 2009, submission also constituted a complete response to S-013. On December 3, 2009, Merck submitted an amended PI, containing further modifications to the language regarding pancreatitis, as requested by FDA. In concurrence with the Office of Chief Counsel (b) (4)

This review is in reference to the changes made to the Package Insert and the Carton and Container labeling and the addition of a REMS and Medication Guide, under S-010, S-011, S-012 and S-014.

Review of Package Insert

The PI, submitted on February 17, 2010, was compared to the currently approved PI for Januvia submitted on December 3, 2009 and approved on December 28, 2009. The following changes were found:

OVERALL

- The identifying number at the top of each page was changed from **"97627XX" to "XXXXXX"**.
- The header on each page has been changed from **"JANUVIA™"** to **"JANUVIA®"**.
- Four new tables (3, 9, 10 and 12) were added to the Package Insert, resulting in re-numbering of most of the other tables throughout the document.

HIGHLIGHTS OF PRESCRIBING INFORMATION

- Recent Major Changes was changed from:

Indications and Usage	
Important Limitations of Use (1.2)	(b) (4)
Warnings and Precautions	
Pancreatitis (5.1)	(b) (4)

to:

Indications and Usage	
Important Limitations of Use (1.2)	**12/2009**
Dosage and Administration	
Concomitant Use with an Insulin Secretagogue(e.g., Sulfonylurea or	
With Insulin (2.3)	**XX/20XX**
Warnings and Precautions	
Pancreatitis (5.1)	**12/2009**
Use with Medications Known to Cause Hypoglycemia(5.3)	**XX/20XX**

- Under Indications and Usage, Important Limitations of Use, the second bullet point shown below was deleted:

  JANUVIA has not been studied in combination with insulin. (1.2)

- Under Warnings and Precautions, the third bullet point was changed from:

When used with a sulfonylurea, a lower dose of sulfonylurea may be required to reduce the risk of hypoglycemia. (2.3, 5.3)

to:

There is an increased risk of hypoglycemia when JANUVIA is added to an insulin secretagogue (e.g., sulfonylurea) or insulin therapy. Consider lowering the dose of the sulfonylurea or insulin to reduce the risk of hypoglycemia. (2.3, 5.3)

- Under Adverse Reactions, the second sentence was changed from:

  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:

  In the add-on to sulfonylurea and add-on to insulin studies, hypoglycemia was also more commonly reported in patients treated with JANUVIA compared to placebo. (6.1)

- Under Adverse Reactions, the second paragraph was changed from:

  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.

  to:

  To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

- At the end of the Highlights of Prescribing Information, the last sentence was changed from:

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

  to:

  See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.

- (b) (4)

FULL PRESCRIBING INFORMATION: CONTENTS

- Under Dosage and Administration, sub-section 2.3 was changed from

  Concomitant Use with a Sulfonylurea

  to:

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

FULL PRESCRIBING INFORMATION

- Under Indications and Usage, Important Limitations of Use, the second bullet point shown below was deleted:

  JANUVIA has not been studied in combination with insulin.

- Under Dosage and Administration, sub-section 2.3 was changed from:

  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 (5.3).]***

  to:

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

- The Contraindications section was changed from:

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

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

- Under Warnings and Precautions, sub-section Use with Medications Known to Cause Hypoglycemia 5.3 was changed from:

  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 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).]***

to:

When JANUVIA was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin. ***[See Adverse Reactions (6.1).]*** **Therefore, a lower dose of sulfonylurea or insulin may be required to reduce the risk of hypoglycemia.** ***[See Dosage and Administration (2.3).]***

- Under Adverse Reactions, subsection Clinical Trials Experience (6.1) was changed from:

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.

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.

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

to:

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

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

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

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

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

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

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

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

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

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

Hypoglycemia

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

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

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

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

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

- Under Adverse Reactions, Clinical Trials Experience (6.1), Table 1 was changed from:

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

to:

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

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

† Intent to treat population

- Under Adverse Reactions, Clinical Trials Experience (6.1), the following new Table 3 was added:

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

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

[†] Adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia; a concurrent glucose measurement was not required; intent to treat population.
[‡] Based on total number of events (i.e., a single patient may have had multiple events).
[§] Severe events of hypoglycemia were defined as those events requiring medical assistance or exhibiting depressed level/loss of consciousness or seizure.

- Under Use in Specific Populations, Pregnancy, the fifth sentence was changed from:

  Merck & Co., Inc. maintains a registry to monitor the pregnancy outcomes of women exposed to JANUVIA while pregnant.

  to:

  Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., maintains a registry to monitor the pregnancy outcomes of women exposed to JANUVIA while pregnant.

- Under Clinical Studies, the first paragraph was changed from:

  There were approximately 3800 patients with type 2 diabetes randomized in six double-blind, placebo-controlled clinical safety and efficacy studies conducted to evaluate the effects of sitagliptin on glycemic control. The ethnic/racial distribution in these studies was approximately 60% white, 20% Hispanic, 8% Asian, 6% black, and 6% other groups. Patients had an overall mean age of approximately 55 years (range 18 to 87 years). In addition, an active (glipizide)-controlled study of 52-weeks duration was conducted in 1172 patients with type 2 diabetes who had inadequate glycemic control on metformin.

  to:

  There were approximately 5200 patients with type 2 diabetes randomized in nine double-blind, placebo-controlled clinical safety and efficacy studies conducted to evaluate the effects of sitagliptin on glycemic control. In a pooled analysis of seven of these studies, the ethnic/racial distribution was approximately 59% white, 20% Hispanic, 10% Asian, 6% black, and 6% other groups. Patients had an overall mean age of approximately 55

years (range 18 to 87 years). In addition, an active (glipizide)-controlled study of 52-weeks duration was conducted in 1172 patients with type 2 diabetes who had inadequate glycemic control on metformin.

- Under Clinical Studies, Combination Therapy (14.2), the following two sub-sections and Tables 9 and 10 were added:

Initial Combination Therapy with Pioglitazone

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

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

Table 9
Glycemic Parameters at Final Visit (24-Week Study)
for JANUVIA in Combination with Pioglitazone as Initial Therapy[†]

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

[†] Intent to Treat Population using last observation on study.
[‡] Least squares means adjusted for baseline value.
[§] $p<0.001$ compared to placebo + pioglitazone.

Add-on Combination Therapy with Metformin and Rosiglitazone

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

In combination with metformin and rosiglitazone, JANUVIA provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo with metformin and rosiglitazone (Table 10) at Week 18. At Week 54, mean reduction in A1C was -1.0% for patients treated with JANUVIA and -0.3% for patients treated with placebo in an analysis based on the intent to treat population. Rescue therapy was used in 18% of patients treated with JANUVIA 100 mg and 40% of patients treated with placebo. There was no significant difference between JANUVIA and placebo in body weight change.

Table 10
Glycemic Parameters at Week 18
for JANUVIA in Add-on Combination Therapy with Metformin and Rosiglitazone[†]

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

[†] Intent to Treat Population using last observation on study prior to glipizide (or other sulfonylurea) rescue therapy.
[‡] Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
[§] $p<0.001$ compared to placebo + metformin + rosiglitazone.

- Under Clinical Studies, Combination Therapy (14.2), the title of Table 11 (previously Table 8), was changed from:

  Glycemic Parameters at Final Visit (24-Week Study) for JANUVIA in Combination with Glimepiride, with or without Metformin[†]

  to:

  Glycemic Parameters at Final Visit (24-Week Study) for JANUVIA as Add-On Combination Therapy with Glimepiride, with or without Metformin[†]

- Under Clinical Studies, Combination Therapy (14.2), the following sub-section and Table 12 were added:

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

  A total of 641 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of JANUVIA as add-on to insulin therapy (with or without metformin). The racial distribution in this study was approximately 70% white, 18% Asian, 7% black, and 5% other groups. Approximately 14% of the patients in this study were Hispanic. Patients entered a 2-week, single-blind run-in treatment period on pre-mixed, long-acting, or intermediate-acting insulin, with or without metformin (≥1500 mg per day). Patients using short-acting insulins were excluded unless the short-acting insulin was administered as part of a pre-mixed insulin. After the run-in period, patients with inadequate glycemic control (A1C 7.5% to 11%) were randomized to the addition of either 100 mg of JANUVIA or placebo, administered once daily. Patients were on a stable dose of insulin prior to enrollment with no changes in insulin dose permitted during the run-in period. Patients who failed to meet specific glycemic goals during the double-blind treatment period were to have uptitration of the background insulin dose as rescue therapy.

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

Table 12
Glycemic Parameters at Final Visit (24-Week Study)
for JANUVIA as Add-on Combination Therapy with Insulin[†]

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

[†] Intent to Treat Population using last observation on study prior to rescue therapy.
[‡] Least squares means adjusted for metformin use at the screening visit (yes/no), type of insulin used at the screening visit (pre-mixed vs. non-pre-mixed [intermediate- or long-acting]), and baseline value.
[§] Treatment by stratum interaction was not significant (p>0.10) for metformin stratum and for insulin stratum.
[¶] p<0.001 compared to placebo.

- Under Patient Counseling Information (17), the first sentence was changed from:

  [redacted] (b) (4)

  to:

  See FDA-Approved Medication Guide.

- Under Patient Counseling Information, Instructions (17.1), the following was added as a third paragraph:

  Patients should be informed that the incidence of hypoglycemia is increased when JANUVIA is added to a sulfonylurea or insulin and that a lower dose of the sulfonylurea or insulin may be required to reduce the risk of hypoglycemia.

- Under Patient Counseling Information, Instructions (17.1), the first sentence of the fourth paragraph was changed from:

  [redacted] (b) (4)

  to:

  Physicians should instruct their patients to read the Medication Guide before starting

JANUVIA therapy and to reread each time the prescription is renewed.

END OF PACKAGE INSERT

- The first two lines were changed from the following text:

  Manufactured for:
  K MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

  To the following graphic:

- The identifying number was changed from [redacted] (b) (4) to **"XXXXXX"**.

- The last three lines were changed from:

  [1]Trademark of MERCK & CO., Inc., Whitehouse Station, New Jersey 08889 USA
  COPYRIGHT © 2006, 2007, 2009 MERCK & CO., Inc.
  All rights reserved

  to:

  [1] Registered trademark of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
  Copyright © 2006, 2007, 2009 Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
  All rights reserved.

Review of Carton and Container Labeling

The representative carton and container labeling, submitted on February 23, 2010, was compared to the currently approved carton and container labeling for Januvia submitted on March 28, 2008 and approved on September 26, 2008. The following changes were found:

- In the representative Trade Container (100 mg – 30 Tablets), the following text was added in bold font to the right column of the label:

  Dispense the accompanying Medication Guide to each patient.

- In the representative Trade Container label (100 mg – 30 Tablets), the manufacturing information at the bottom of the right column was changed from:

  to:

  Manuf. for: Merck Sharp & Dohme Corp.,
  a subsidiary of Merck & Co., Inc.
  Whitehouse Station, NJ 08889, USA
  Manuf. by: Merck Sharp & Dohme (Italia) S.p.A.
  Via Emilia, 21, 27100–Pavia, Italy
  Made in Italy.

- In the representative Physician Sample Carton label (100 mg – 28 Tablets), the text in the right column of the main panel of the label was changed from:

to:

Dispense the enclosed Medication Guide to each patient (in bold font)
See the accompanying circular for dosage information.

- In the representative Physician Sample Carton label (100 mg – 28 Tablets), the following text was added to the side panel of the label:

Manuf. for:
Merck Sharp & Dohme Corp, Inc.
a subsidiary of
MERCK & Co, Inc.
Whitehouse Station, NJ 08889, USA

Manuf. by:
Merck Sharp & Dohme (Italia) S.p.A.
Via Emilia, 21
27100 – Pavia, Italy
Made in Italy

Conclusion

All changes were found acceptable, as documented in the reviews in DARRTS dated September 2 and 3, and November 17, 2009 (S-010 and S-011), dated November 2 and 10, and December 22, 2009 (S-012) and dated December 18, 2009 (S-014). The REMS (final version submitted on February 19, 2010) and Medication Guide (final version submitted on February 4, 2010) are newly created, and will be attached to the approval letter for S-014.

An approval letter for NDA 21-995/S-010, S-011, S-012 and S-014 should be issued.

Reviewed by:
Mehreen Hai, Ph.D.
Regulatory Project Manager

Supervisory concurrence:
Lina Aljuburi, Pharm.D., M.S.
Chief, Project Management Staff

Drafted: M.Hai/02.25.10
Clearance: L.Aljuburi/02.25.10
Finalized: M.Hai/02.26.10

CSO LABELING REVIEW

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21995	SUPPL-10	MERCK CO INC	JANUVIA 100MG (SITAGLIPTIN PHOSPHATE)
NDA-21995	SUPPL-11	MERCK CO INC	JANUVIA 100MG (SITAGLIPTIN PHOSPHATE)
NDA-21995	SUPPL-12	MERCK CO INC	JANUVIA 100MG (SITAGLIPTIN PHOSPHATE)
NDA-21995	SUPPL-14	MERCK CO INC	JANUVIA 100MG (SITAGLIPTIN PHOSPHATE)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MEHREEN HAI
02/26/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021995/S-014

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021995/S-014

Merck & Co., Inc.
Attention: Richard J. Swanson, Ph.D.
Director, Regulatory Affairs
P.O. Box 1000, UG2C-50
North Wales, PA 19454-1099

Dear Dr. Swanson:

Please refer to your supplemental new drug application (sNDA-014) dated and received November 13, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Januvia (sitagliptin) tablets.

On October 16, 2009, we sent you a letter invoking our authority under section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FDCA) to require safety related label changes to the labeling of Januvia (sitagliptin) to address the risk of acute pancreatitis, including necrotizing pancreatitis, with the use of Januvia (sitagliptin), based on new safety information about this risk identified since the product was approved. You were directed to submit a prior approval supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

On November 13, 2009, FDA received your prior approval supplement that contained your proposed safety related labeling changes, including a newly created Medication Guide. Section 505(o) requires FDA to promptly review the supplement and if we disagree with the proposed changes, to initiate discussions with you on the content of the changes. These discussions were to be completed within 30 days, unless FDA determined that an extension was warranted.

We refer to the letter we sent to you on December 28, 2009, informing you that we determined that a 30-day extension of the discussion period was warranted to allow us to complete our review and reach agreement on the content of the Medication Guide portion of the labeling.

This letter is to inform you that we have determined that an additional 30-day extension of the discussion period is warranted. Therefore, the discussion period for this supplement, NDA 021995/S-014 ends on February 11, 2010.

If you have any questions, please call Mehreen Hai, Ph.D., Regulatory Project Manager, at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21995	SUPPL-14	MERCK CO INC	JANUVIA 100MG (SITAGLIPTIN PHOSPHATE)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY H PARKS
01/27/2010

From:	Hai, Mehreen
To:	"Swanson, Richard John";
Subject:	MedGuides and REMS
Date:	Wednesday, January 13, 2010 9:23:12 AM
Attachments:	Januvia-Janumet REMS-FDA comments-13Jan10.pdf Januvia Medication Guide - final.doc Janumet Medication Guide - final.doc

---

Hi Rick,
Please find attached our proposed revisions for the Januvia and Janumet MedGuides (Word files), as well as our comments and proposed revisions to the REMS for Januvia and Janumet (PDF file).

Please let me know if you have any questions.

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

See the appended JANUMET (sitagliptin/metformin HCl) and JANUVIA (sitagliptin phosphate) REMS proposal for track changes corresponding to the comments below.

a. GOAL

   Revise your goal as follows:

   The goal of this REMS is to inform patients about the serious risk associated with the use of JANUMET (sitagliptin/metformin HCl) or JANUVIA (sitagliptin phosphate).

b. We acknowledge your proposal to provide sufficient numbers of Medication Guides such that a dispenser can provide one Medication Guide with each new or refilled prescription. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each "usual" or average dose. For example:

   - A minimum of 4 Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.
   - A minimum of 1 Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.

c. Your proposed timetable for submission of assessments 18 months, 3 years, and 7 years is acceptable.

   We have some editorial comments in this section of the proposed REMS.

d. Please submit for review a detailed plan to evaluate patients' understanding about the safe use of JANUMET (sitagliptin/metformin HCL) or JANUVIA (sitagliptin). Your detailed plan should be submitted as part of the REMS supporting document. This information **does not** need to be submitted for FDA review prior to approval of your REMS, however it should be submitted at least 90 days before you plan to conduct the evaluation. The submission should be coded "REMS Correspondence." If you plan to conduct this assessment using a survey, your submission should include:

- All methodology and instruments that will be used to evaluate the patients' understanding about the safe use of JANUMET (sitagliptin/metformin HCL) or JANUVIA (sitagliptin). This should include, but not be limited to:

  - Sample size and confidence associated with that sample size
  - How the sample will be determined (selection criteria)
  - The expected number of patients to be surveyed
  - How the participants will be recruited

    - How and how often the surveys will be administered
    - Explain controls used to minimize bias
    - Explain controls used to compensate for the limitations associated with the methodology

- The survey instruments (questionnaires and/or moderator's guide).
- Any background information on testing survey questions and correlation to the messages in the Medication Guide.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21995	SUPPL-14	MERCK CO INC	JANUVIA 100MG (SITAGLIPTIN PHOSPHATE)
NDA-22044	SUPPL-13	MERCK AND CO INC	JANUMET(PHOSPHATE/METFORMIN HCL FIXED DO

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MEHREEN HAI
01/13/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-995/S-013, S-014

PRIOR APPROVAL SUPPLEMENT
COMPLETE RESPONSE – LABELING

Merck & Co., Inc.
Attention: Richard J. Swanson, Ph.D.
Director, Regulatory Affairs
P.O. Box 1000, UG2C-50
North Wales, PA 19454-1099

Dear Dr. Swanson:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Januvia (sitagliptin) Tablets
NDA Number:	21-995
Supplement number:	S-014
Date of supplement:	November 13, 2009
Date of receipt:	November 13, 2009

This supplemental application also constitutes a complete response to our October 16, 2009, action letter for supplemental application S-013. S-013 proposes the addition of "cutaneous vasculitis" and "pancreatitis" to the Postmarketing Experience subsection of the Adverse Reactions section of the package insert, and proposes the addition of "inflammation of the pancreas" to the patient package insert.

In response to the safety labeling change request outlined in our October 16, 2009, action letter, S-014 proposes the addition of information regarding pancreatitis in the Highlights of Prescribing Information section, subsection Important Limitations of Use and subsection Warnings and Precautions, as well as in the corresponding subsections of the Full Prescribing Information section of the package insert. In addition, in accordance with our action letter, this submission also contains a Risk Evaluation and Mitigation Strategy (REMS), as well as a newly created Medication Guide.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 12, 2010, in accordance with 21 CFR 314.101(a).

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21995	SUPPL-13	MERCK CO INC	JANUVIA 100MG (SITAGLIPTIN PHOSPHATE)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MEHREEN HAI
12/28/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
CDER OSE Consults
Margarita Tossa
Office of Safety and Epidemiology
Email: margarita.tossa@fda hhs.gov
WO22 RM 3461, Phone: 796-4053

FROM:
Mehreen Hai
Regulatory Project Manager
DMEP, HFD-510, Phone: 796-5073

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
November 17, 2009		21-995	REMS/Medguide	November 13, 2009

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Januvia	Standard	Treatment of Type II Diabetes	November 19, 2009

NAME OF FIRM: Merck

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☑ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☑ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
Merck has submitted new labeling supplements for Januvia and Janumet containing FDAAA-mandated SLC with a REMS (PPI to MG conversion). Please review the MedGuide and REMS. We need the REMS reviewed by COB Thursday (November 19). Please let me what the turnaround time for the Medguide review is going to be.

The submission is in the EDR dated November 13, 2009.

Januvia (NDA 21-995):
EDR Location: \\CDSESUB1\EVSPROD\NDA021995\021995.enx
Cover letter: \\CDSESUB1\EVSPROD\NDA021995\\0096\m1\us\cover-letter.pdf

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Mehreen Hai	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21995	TRIAGE-1	MERCK CO INC	JANUVIA 100MG (SITAGLIPTIN PHOSPHATE)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MEHREEN HAI
11/17/2009