

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**NDA 021995/S-013**

***Trade Name:* JANUVIA**

***Generic Name:* Sitagliptin**

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

***Approval Date:* 12/28/2009**

***Indications:*** JANUVIA is 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-013**

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**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*  
**NDA 021995/S-013**

**APPROVAL LETTER**



NDA 021995/S-013

**SUPPLEMENT APPROVAL**

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 (S-013) dated and received March 5, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Januvia (sitagliptin) tablets.

We also refer to your supplemental new drug application (b) (4) dated and received November 13, 2009. Your submission of November 13, 2009, also constitutes a complete response to our October 16, 2009, action letter for supplemental application S-013.

In addition, we acknowledge receipt of your submissions dated December 3 and 9, 2009.

**SAFETY LABELING CHANGES**

Our letter dated October 16, 2009, notified you, under section 505(o)(4) of the FDCA, of new safety information that needs to be included in the labeling for Januvia (sitagliptin) tablets. This information pertains to the risk of acute pancreatitis, including necrotizing pancreatitis, with the use of Januvia (sitagliptin).

In response to the safety labeling change requirement outlined in our October 16, 2009, action letter, S-013 (b) (4) propose 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. The agreed-upon changes to the language included in our October 16, 2009, letter are as follows (additions are noted by underline and deletion are noted by ~~striketrough~~):

1. In the section Highlights of Prescribing Information, sub-section Indications and Usage, Important Limitations of Use, the following has been added:

**JANUVIA has not been studied in patients with a history of pancreatitis.**

(b) (4)

(1. (b) (4) **5.1**).

2. In the section Highlights of Prescribing Information, sub-section Warnings and Precautions, the following has been added:

(b) (4) **There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. If pancreatitis is suspected, promptly discontinue JANUVIA.**

(b) (4)

(5.1).

3. In the section Full Prescribing Information, sub-section 1.2 Important Limitations of Use, the following has been added:

(b) (4)  
**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).]**

(b) (4)

4. In the section Full Prescribing Information, sub-section 5. Warnings and Precautions, the following has been added:

(b) (4)  
**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,**

(b) (4)

**patients should be observed carefully for signs and symptoms of pancreatitis**

(b) (4)

**. 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.**

(b) (4)

Additional agreed upon changes to the package insert include:

5. Under Adverse Reactions, Postmarketing Experience (6.2), the following has been added:

**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)].**

6. Under Patient Counseling Information, Instructions (17.1), the following has been added as a second paragraph:

**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)].**

The Package Insert is approved under S-013, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with the minor editorial revisions listed below.

1. At the end of the Highlights of Prescribing Information section, remove the reference to the FDA-approved patient labeling or Medication Guide, as the Medication Guide has not yet been approved for circulation. When the Medication Guide is approved, this text can be re-inserted in the PI.
2. Under Patient Counseling Information (17), remove the reference to the FDA-approved patient labeling or Medication Guide (see comment #1 above).
3. Under Patient Counseling Information, Instructions (17.1), remove the reference to the FDA-approved patient labeling or Medication Guide (see comment #1 above).

As soon as possible, but no later than 14 days from the date of this letter, submit the package insert [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). For administrative purposes, please designate this submission, "SPL for approved NDA 021995/S-013". Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

(b) (4)

### **RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

Our October 16, 2009, letter also notified you that, based on new safety information regarding the risk of acute pancreatitis, including necrotizing pancreatitis, with use of Januvia (sitagliptin), a Risk Evaluation and Mitigation Strategy (REMS) which consists of a Medication Guide and timetable for submission of the assessments of the REMS, is required for Januvia (sitagliptin).

(b) (4)

### **CARTON AND IMMEDIATE CONTAINER LABELS**

We acknowledge your November 13, 2009, submission containing draft carton and container labels.

(b) (4)

### **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

Enclosure: Package Insert

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

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/s/  
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ERIC C COLMAN  
12/28/2009  
Eric Colman for Mary Parks

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*  
**NDA 021995/S-013**

**OTHER ACTION LETTERS**



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)

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/s/

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MEHREEN HAI  
12/28/2009



NDA 21-995/S-010, S-011, S-013

**COMPLETE RESPONSE**

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 applications (sNDAs) dated and received December 18 (S-010) and 19 (S-011), 2008, and March 5, 2009 (S-013), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Januvia (sitagliptin) tablets.

We acknowledge receipt of your amendments dated April 3, 9, 13, and 14, May 5, June 8, and September 25, 2009 (S-010); April 10 and June 8, 2009 (S-011); and April 1, May 4 and 6, and September 25, 2009 (S-013).

These "Prior Approval" supplemental applications provide for the use of Januvia (sitagliptin) as combination therapy with a PPAR $\gamma$  agonist (S-011) and for the use of Januvia (sitagliptin) in combination with metformin and a PPAR $\gamma$  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 PPAR $\gamma$  agonist (S-010).

The "Changes Being Effected in 30 days" supplemental new drug application (S-013) provides for 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.

We have completed the review of your applications and have been unable to reach agreement with you regarding the extent and placement of the information about pancreatitis in the product label for Januvia (sitagliptin). Therefore, we have determined that we cannot approve these applications in their present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

Sections 505(o)(4) and 505-1 of the FDCA authorize FDA to require holders of approved drug and biological product applications to make safety related labeling changes and develop and comply with Risk Evaluation and Mitigation Strategies (REMS) based upon new safety information that becomes available after approval of the drug or biological product.

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 section 505-1(b)(3) of the FDCA.

## **SAFETY LABELING CHANGES**

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above, we believe that the new safety information should be included in the labeling for Januvia (sitagliptin) as follows:

1. In the section Highlights of Prescribing Information, sub-section Indications and Usage, Important Limitations of Use, add the following:

**JANUVIA has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis (1.2).**

2. In the section Highlights of Prescribing Information, sub-section Warnings and Precautions, add the following:

**Pancreatitis: Postmarketing reports, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. *Discontinue JANUVIA promptly. JANUVIA should not be restarted.* Consider other antidiabetic therapies in patients with a history of pancreatitis (5.1).**

3. In the section Full Prescribing Information, sub-section 1.2 Important Limitations of Use, add the following:

**Based on post-marketing data JANUVIA has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. 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 pancreatitis while using JANUVIA. Other antidiabetic therapies should be considered in patients with a history of pancreatitis.**

4. In the section Full Prescribing Information, sub-section 5. Warnings and Precautions, add the following:

**Based on post-marketing data, JANUVIA has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. After initiation of JANUVIA, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting). If pancreatitis is suspected, JANUVIA should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, JANUVIA should not be restarted. Consider**

**antidiabetic therapies other than JANUVIA in patients with a history of pancreatitis.**

Medication Guide

In addition to the changes described above to the labeling, you should convert your patient package insert to a Medication Guide for Januvia (sitagliptin). Your Medication Guide must include information about the serious risk of pancreatitis and will be considered part of the proposed REMS described below.

**RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

In accordance with section 505-1(a) of the FDCA, we have determined that a REMS is necessary for Januvia (sitagliptin) to ensure that the benefits of the drug outweigh the risks based on the new safety information described above.

Your proposed REMS must include the following:

**Medication Guide:** As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Januvia (sitagliptin) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Januvia (sitagliptin). FDA has determined that Januvia (sitagliptin) is a product for which patient labeling could help prevent serious adverse effects and has a serious risk (relative to benefits) of which patients should be made aware because information concerning the risk could affect patients' decisions to use, or continue to use Januvia (sitagliptin).

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Januvia (sitagliptin).

Your previously approved patient package insert must be converted to a Medication Guide and must be revised to include the new safety information.

**Timetable for Submission of Assessments:** The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than by 18 months, 3 years, and in the 7<sup>th</sup> year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. 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. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

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

Please note that supplemental application NDA 21-995/S-013 was submitted as a "Changes Being Effected in 30 days" supplement. We will consider this supplement a Prior Approval Supplement. The above changes to the proposed labeling cannot be put into effect prior to approval of a supplement. An approved supplement is required for these proposed changes prior to distributing drug product made with these changes.

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit to your supplements noted above proposed 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. In accordance with section 505-1, you must also submit a proposed REMS within 30 days of the date of this letter. The submission statement about the safety labeling change and the proposed REMS should be included in the same submission.

Your proposed REMS submission includes two parts: a "proposed REMS" and a "REMS supporting document." Attached is a template for the Proposed REMS that you should complete with concise, specific information (see Appendix A). Once FDA finds the content acceptable, we will include this document and the Medication Guide as attachments to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

The safety labeling changes portion of the supplement should contain the Medication Guide for Januvia (sitagliptin). Include labeling in both Microsoft Word format and content of labeling (21 CFR 314.50(1) in structured product labeling (SPL) format as described at: <http://www.fda.gov/oc/datacouncil/spl.html>.

Under 21 CFR 208.24(d), you are also responsible for ensuring that the label of each container or package, where the container label is too small, includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. The safety labeling changes portion of the supplement should contain marked up package or container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- "Dispense the enclosed Medication Guide to each patient." or
- "Dispense the accompanying Medication Guide to each patient."

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**NEW SUPPLEMENT FOR NDA 21-995/S-010, S-011, S-013  
PROPOSED REMS  
AND  
SAFETY LABELING CHANGES UNDER 505(o)(4) )-PRIOR APPROVAL  
SUPPLEMENT  
OR  
SAFETY LABELING CHANGES UNDER 505(o)(4)- CHANGE NOT WARRANTED**

Prominently identify subsequent submissions related to the proposed REMS and/or the safety labeling changes with the following wording in bold capital letters at the top of the first page of the submission:

**SUPPLEMENT NDA 21-995/S-010, S-011, S-013  
PROPOSED REMS-AMENDMENT  
AND/OR  
SUPPLEMENT NDA 21-995/S-010, S-011, S-013  
SAFETY LABELING CHANGES UNDER 505(o)(4) - AMENDMENT**

If you do not submit electronically, please send 5 copies of your submission.

**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)).

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 will be required, pursuant to section 505(o)(3) of the FDCA, to conduct the following study if your application is approved:

1. A 3-month pancreatic safety study in a diabetic rodent model treated with sitagliptin.

The specific details of this required postmarketing study will be described more fully in the approval letter for these applications, if they are approved.

## **SAFETY UPDATE**

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
  - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
  - Present tabulations of the new safety data combined with the original NDA data.
  - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

## **OTHER**

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A

resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of the "Prior Approval" supplemental application.

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:

Appendix A – REMS template

Appendix B – REMS Supporting Document template

**APPENDIX A: MEDICATION GUIDE REMS TEMPLATE**

**Application number TRADE NAME (DRUG NAME)**

Class of Product as per label

Applicant name

Address

Contact Information

**RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

**I. GOAL(S):**

List the goals and objectives of the REMS.

**II. REMS ELEMENTS:**

**A. Medication Guide**

*If a Medication Guide is included in the proposed REMS, include the following:*

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

**B. Timetable for Submission of Assessments**

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18 months, 3 years, and in the 7<sup>th</sup> year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. 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. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

**APPENDIX B:**  
**REMS SUPPORTING DOCUMENT TEMPLATE**  
**MEDICATION GUIDE REMS**

This REMS Supporting Document should include the following listed sections 1 through 6. Include in section 4 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents
2. Background
3. Goals
4. Supporting Information on Proposed REMS Elements
  - a. Medication Guide
  - b. Timetable for Submission of Assessments of the REMS (for products approved under an NDA or BLA)
5. REMS Assessment Plan (for products approved under a NDA or BLA)
6. Other Relevant Information

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-13	MERCK CO INC	JANUVIA 100MG (SITAGLIPTIN PHOSPHATE)

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/s/

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AMY G EGAN  
10/16/2009  
Amy Egan for Mary Parks

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**NDA 021995/S-013**

**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) xx/20xx  
Warnings and Precautions  
Pancreatitis (5.1) xx/20xx

**INDICATIONS AND USAGE**

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

**Important Limitations of Use:**

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

**DOSAGE AND ADMINISTRATION**

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

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

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

**DOSAGE FORMS AND STRENGTHS**

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

**CONTRAINDICATIONS**

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

**WARNINGS AND PRECAUTIONS**

- There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. If pancreatitis is suspected, promptly discontinue JANUVIA. (5.1)
- 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)
- When used with a sulfonylurea, a lower dose of sulfonylurea may be required 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  $\geq$ 5% of patients treated with JANUVIA and more commonly than in patients treated with placebo are: upper respiratory tract infection, nasopharyngitis and headache. Hypoglycemia was also reported more commonly in patients treated with the combination of JANUVIA and sulfonylurea, with or without metformin, than in patients given the combination of placebo and sulfonylurea, with or without metformin. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Merck & Co., Inc. at 1-877-888-4231 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

**USE IN SPECIFIC POPULATIONS**

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

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

Revised: xx/20xx

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 Monotherapy and Combination Therapy

JANUVIA<sup>1</sup> is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. [See *Clinical Studies (14).*]

#### 1.2 Important Limitations of Use

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

JANUVIA has not been studied in combination with insulin.

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

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

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

Because there is a need for dosage adjustment based upon renal function, assessment of renal function is recommended prior to initiation of JANUVIA and periodically thereafter. Creatinine clearance can be estimated from serum creatinine using the Cockcroft-Gault formula. [See *Clinical Pharmacology (12.3).*]

#### 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).*]

### 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)* and *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**

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)*.]

### **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 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  $\geq 5\%$  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.

**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<sup>†</sup>**

Monotherapy	Number of Patients (%)	
	JANUVIA 100 mg	Placebo
	N = 443	N = 363
Nasopharyngitis	23 (5.2)	12 (3.3)
Combination with Pioglitazone	JANUVIA 100 mg + Pioglitazone	Placebo + Pioglitazone
	N = 175	N = 178
Upper Respiratory Tract Infection	11 (6.3)	6 (3.4)
Headache	9 (5.1)	7 (3.9)
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)

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

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

In the prespecified pooled analysis of the two monotherapy studies, the add-on to metformin study, and the add-on to pioglitazone study, the overall incidence of adverse reactions of hypoglycemia in patients treated with JANUVIA 100 mg was similar to placebo (1.2% vs 0.9%). Adverse reactions of hypoglycemia were based on all reports of hypoglycemia; a concurrent glucose measurement was not required. The incidence of selected gastrointestinal adverse reactions in patients treated with JANUVIA was as follows: abdominal pain (JANUVIA 100 mg, 2.3%; placebo, 2.1%), nausea (1.4%, 0.6%), and diarrhea (3.0%, 2.3%).

In an additional, 24-week, placebo-controlled factorial study of initial therapy with sitagliptin in combination with metformin, the adverse reactions reported (regardless of investigator assessment of causality) in ≥5% of patients are shown in Table 2. The incidence of hypoglycemia was 0.6% in patients given placebo, 0.6% in patients given sitagliptin alone, 0.8% in patients given metformin alone, and 1.6% in patients given sitagliptin in combination with metformin.

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

	Number of Patients (%)			
	Placebo	Sitagliptin (JANUVIA) 100 mg QD	Metformin 500 or 1000 mg bid <sup>††</sup>	Sitagliptin 50 mg bid + Metformin 500 or 1000 mg bid <sup>††</sup>
	N = 176	N = 179	N = 364 <sup>††</sup>	N = 372 <sup>††</sup>
Upper Respiratory Infection	9 (5.1)	8 (4.5)	19 (5.2)	23 (6.2)
Headache	5 (2.8)	2 (1.1)	14 (3.8)	22 (5.9)

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

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

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

#### Laboratory Tests

Across clinical studies, the incidence of laboratory adverse reactions was similar in patients treated with JANUVIA 100 mg compared to patients treated with placebo. A small increase in white blood cell count (WBC) was observed due to an increase in neutrophils. This increase in WBC (of approximately

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 & 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.

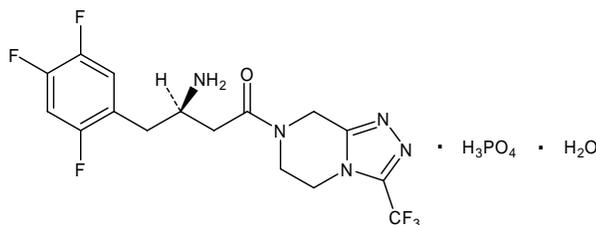
Sitagliptin is modestly dialyzable. In clinical studies, approximately 13.5% of the dose was removed over a 3- to 4-hour hemodialysis session. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialyzable by peritoneal dialysis.

## 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<sub>16</sub>H<sub>15</sub>F<sub>6</sub>N<sub>5</sub>O•H<sub>3</sub>PO<sub>4</sub>•H<sub>2</sub>O and the molecular weight is 523.32. The structural formula is:



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

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

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

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

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

## 12.2 Pharmacodynamics

### General

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

In a two-day study in healthy subjects, sitagliptin alone increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. 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  $\mu\text{M}\cdot\text{hr}$ ,  $C_{max}$  was 950 nM, and apparent terminal half-life ( $t_{1/2}$ ) was 12.4 hours. Plasma AUC of sitagliptin increased approximately 14% following 100 mg doses at steady-state compared to the first dose. The intra-subject and inter-subject coefficients of variation for sitagliptin AUC were small (5.8% and 15.1%). The pharmacokinetics of sitagliptin was generally similar in healthy subjects and in patients with type 2 diabetes.

### Absorption

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

### Distribution

The mean volume of distribution at steady state following a single 100 mg intravenous dose of sitagliptin to healthy subjects is approximately 198 liters. The fraction of sitagliptin reversibly bound to plasma proteins is low (38%).

### *Metabolism*

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

Following a [<sup>14</sup>C]sitagliptin oral dose, approximately 16% of the radioactivity was excreted as metabolites of sitagliptin. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. *In vitro* studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.

### *Excretion*

Following administration of an oral [<sup>14</sup>C]sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in feces (13%) or urine (87%) within one week of dosing. The apparent terminal  $t_{1/2}$  following a 100 mg oral dose of sitagliptin was approximately 12.4 hours and renal clearance was approximately 350 mL/min.

Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), which may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of p-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. However, cyclosporine, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin.

### *Special Populations*

#### *Renal Insufficiency*

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

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

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

#### *Hepatic Insufficiency*

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

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 3). 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 3**  
**Glycemic Parameters in 18- and 24-Week Placebo-Controlled Studies of JANUVIA in Patients with Type 2 Diabetes<sup>†</sup>**

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

<sup>†</sup> Intent to Treat Population using last observation on study prior to metformin rescue therapy.

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

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

|| 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 4). 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 4**  
**Glycemic Parameters at Final Visit (24-Week Study)**  
**for JANUVIA in Add-on Combination Therapy with Metformin<sup>†</sup>**

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

<sup>†</sup> Intent to Treat Population using last observation on study prior to pioglitazone rescue therapy.

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

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

#### *Initial Combination Therapy with Metformin*

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

Initial therapy with the combination of JANUVIA and metformin provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo, to metformin alone, and to JANUVIA alone (Table 5, 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 5**  
**Glycemic Parameters at Final Visit (24-Week Study)**  
**for Sitagliptin and Metformin, Alone and in Combination as Initial Therapy<sup>†</sup>**

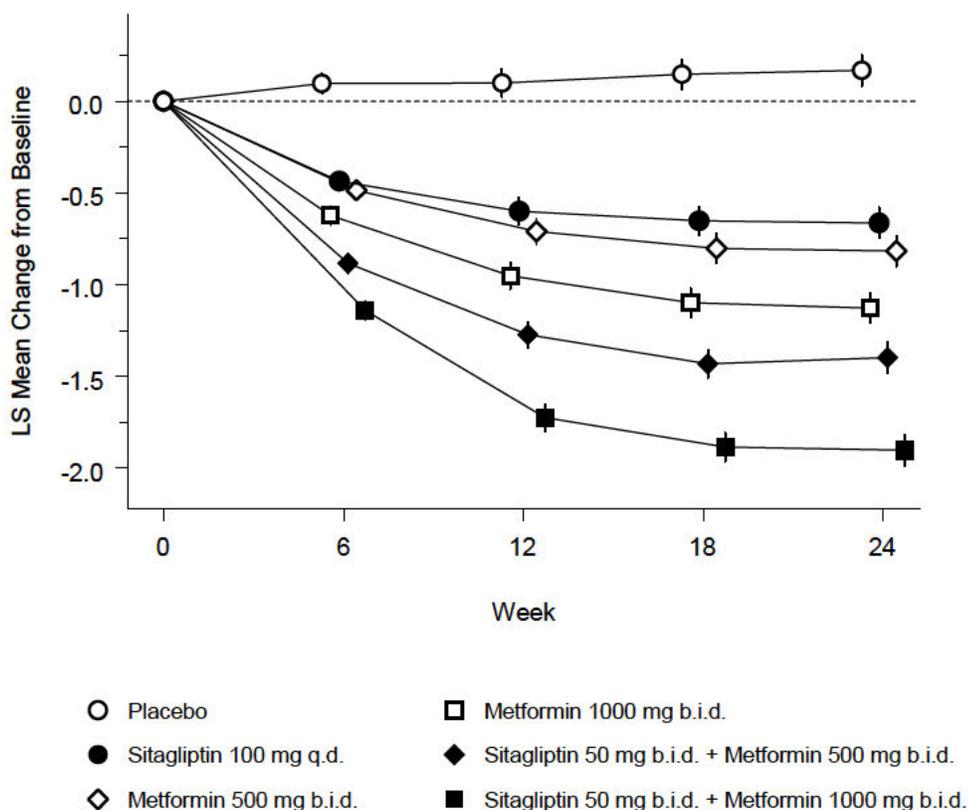
	Placebo	Sitagliptin (JANUVIA) 100 mg QD	Metformin 500 mg bid	Metformin 1000 mg bid	Sitagliptin 50 mg bid + Metformin 500 mg bid	Sitagliptin 50 mg bid + Metformin 1000 mg bid
<b>A1C (%)</b>	<b>N = 165</b>	<b>N = 175</b>	<b>N = 178</b>	<b>N = 177</b>	<b>N = 183</b>	<b>N = 178</b>
Baseline (mean)	8.7	8.9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

<sup>†</sup> Intent to Treat Population using last observation on study prior to glyburide (glibenclamide) rescue therapy.

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

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

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



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

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.

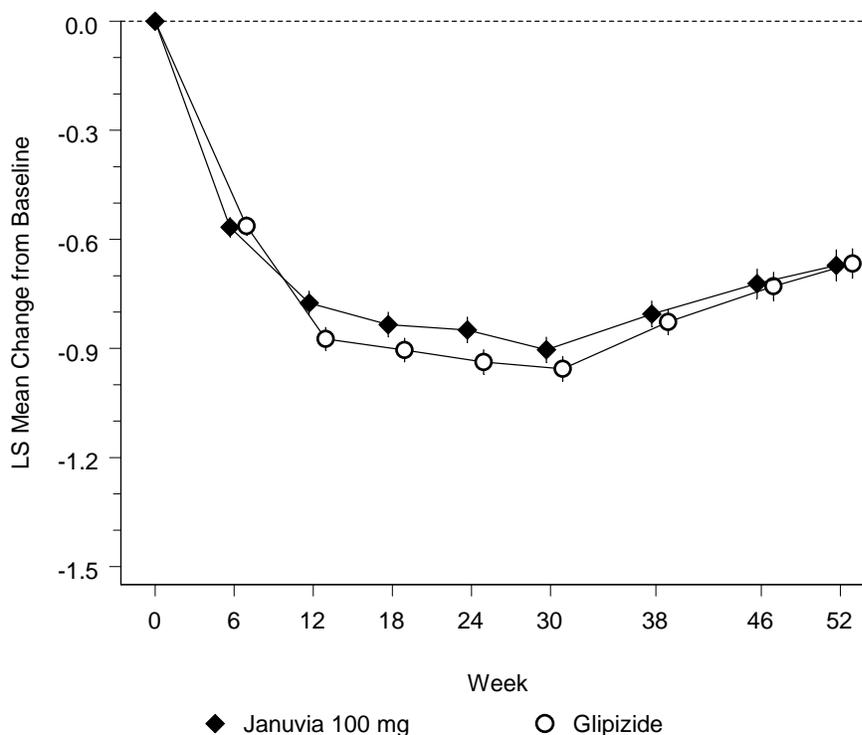
After 52 weeks, JANUVIA and glipizide had similar mean reductions from baseline in A1C in the intent-to-treat analysis (Table 6). These results were consistent with the per protocol analysis (Figure 2). A conclusion in favor of the non-inferiority of JANUVIA to glipizide may be limited to patients with baseline A1C comparable to those included in the study (over 70% of patients had baseline A1C <8% and over 90% had A1C <9%).

**Table 6**  
**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)<sup>†</sup>**

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

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

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



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

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

*Add-on Combination Therapy with Pioglitazone*

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

In combination with pioglitazone, JANUVIA provided significant improvements in A1C and FPG compared to placebo with pioglitazone (Table 7). 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 7**  
**Glycemic Parameters at Final Visit (24-Week Study)**  
**for JANUVIA in Add-on Combination Therapy with Pioglitazone<sup>†</sup>**

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

<sup>†</sup> Intent to Treat Population using last observation on study prior to metformin rescue therapy.

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

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

*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 ( $\geq$ 4 mg per day) alone or glimepiride in combination with metformin ( $\geq$ 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 8). 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 8**  
**Glycemic Parameters at Final Visit (24-Week Study)**  
**for JANUVIA in Combination with Glimepiride, with or without Metformin<sup>†</sup>**

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

<sup>†</sup> Intent to Treat Population using last observation on study prior to pioglitazone rescue therapy.

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

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

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

## 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 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.

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Manufactured for:

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

Manufactured by:

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 021995/S-013**

**MEDICAL REVIEW(S)**

**Clinical Review**

Ilan Irony, M.D.

sNDA 21995 / S-013 and sNDA 22044 / S-011

Januvia™ (Sitagliptin) and Janumet™ (Sitagliptin /metformin FDC)

**CLINICAL REVIEW**

Application Type: NDA

Submission Number: 21995 and 22044

Submission Code: Labeling Supplement CBE

Letter Date: 2009-03-05

Stamp Date: 2009-03-05

PDUFA Goal Date: 2009-09-05

Reviewer Name: Ilan Irony

Through: Mary Parks

Review Completion Date: 2009-08-06

Established Name: Sitagliptin Phosphate

Sitagliptin / metformin fixed-dose combination

Trade Name: Januvia and Janumet

Therapeutic Class: Dipeptidyl Peptidase IV inhibitor

Dipeptidyl peptidase IV inhibitor / biguanide

Applicant: Merck

Priority Designation: S

Formulation: Tablets

Dosing Regimen: 25 mg, 50 mg and 100 mg once daily for Januvia

50 mg / 500 mg and 50 mg /1000 mg twice daily for Janumet

Indication: Improvement in glycemic control

Intended Population: Type 2 diabetes mellitus

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Januvia™ (Sitagliptin) and Janumet™ (Sitagliptin /metformin FDC)

# **1. EXECUTIVE SUMMARY**

Sitagliptin is a member of a new class of anti-diabetic drug products called dipeptidyl peptidase IV (DPP4) inhibitors, approved in the United States in October 2006 for the treatment of type 2 diabetes mellitus. Sitagliptin / metformin as a fixed dose combination (FDC) was approved in March 2007.

Through these two supplemental NDAs (sNDAs), the applicant requests a change in product labeling (changes being effected, or CBE) based on post-marketing observations of cases of pancreatitis and various forms of cutaneous vasculitis. The applicant requests that these adverse reactions be added to the label under Section 6.2 “Postmarketing Experience”.

Similar corresponding changes are requested for the Patient Package Insert. This review document will address the post-marketing reports of cutaneous vasculitis and the medical officer’s recommendations for labeling of sitagliptin and sitagliptin / metformin FDC. The cases of pancreatitis included in this CBE supplement are reviewed in a separate review document.

## **1.1 Recommendation on Regulatory Action**

I recommend approval of the CBE supplement as proposed by the applicant. The term “cutaneous vasculitis” should be added as adverse reaction (AR) to Section 6.2 “Postmarketing Experience”. My recommendation is based on the review of data submitted by the applicant and a consultation received from the Division of Pharmacovigilance I (DPV I) in the Office of Surveillance and Epidemiology (OSE).

## **1.2 Recommendation on Postmarketing Actions**

None.

## **1.3 Summary of Clinical Findings**

### **1.3.1 Merck’s data**

In a search of its Worldwide Adverse Events System (WAES), Merck noted 15 postmarketing reports of cutaneous vasculitis in patients treated with sitagliptin or with sitagliptin / metformin FDC from product launch until February 3<sup>rd</sup>, 2009. These reports prompted the submission of this CBE supplement. Of the 15 reports, 13 were spontaneous and 2 were reported from clinical studies. These reports were mapped to the following MedDRA preferred terms: cutaneous vasculitis (1), leukocytoclastic vasculitis (6), perivascular dermatitis (1), vasculitis (5), vasculitic rash (1), and vascular skin disorder (1). Eight of the 15 reports met the regulatory criteria for a serious report; 7 reports were non-serious. Of the 15 reports, 13 were received for sitagliptin and 2 for sitagliptin / metformin FDC. All 15 reports were received from healthcare providers. Two of the 15 reports described a diagnosis of leukocytoclastic vasculitis confirmed by skin biopsy.

The 15 reports were received from 4 countries: United States (8), France (3), Germany (3) and the Philippines (1). Information regarding age was provided in 11/15 (73 %) reports, median age was 64 years old (range 45 to 88 years of age). Information regarding gender was provided in 14/15 (93%) reports: 6/15 were in females and 8/15 reports were in males. Time to onset was provided in

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9/15 (60%) report, ranging approximately 8 days to approximately 244 days, median 43 days. Information regarding outcome and action taken with regard to sitagliptin or sitagliptin / metformin FDC was provided in 12 of 15 (80%) reports; 8 patients were reported as recovered or recovering and 4 patients were reported as not recovered.

### **1.3.2 OSE data**

The consultation report from DPV I describes 14 cases found in an AERS search that included all terms under the Standardized MedDRA Query – Vasculitis Version 11.1, from the date of U.S. approval of sitagliptin and sitagliptin / metformin FDC until May 20<sup>th</sup>, 2009.

Based on these findings, OSE recommends modification of labeling to include cutaneous vasculitis in the Adverse Reactions - Postmarketing Experience section. OSE will continue to monitor all types of vasculitis.

### **1.3.3 Drug-Drug Interactions**

No drug-drug interactions appear to be relevant as a risk for this adverse reaction.

## **2. INTRODUCTION AND BACKGROUND**

Sitagliptin was approved in the U.S. on October 16<sup>th</sup> 2006, as the first drug in the DPP4 inhibitor class, under the tradename Januvia. On March 30<sup>th</sup>, 2007 the fixed dose combination of sitagliptin and metformin was approved in the US, under the tradename Janumet. DPP4 inhibition improves glycemic control in patients with T2DM due to prolongation of the half-life of endogenous GLP-1, as well as the half life of another DPP4 substrate, glucose-dependent insulinotropic polypeptide. On March 5<sup>th</sup>, 2009 DMEP received from the applicant a labeling supplement for changes being effected (CBE) to add cutaneous vasculitis to the labeling of sitagliptin and sitagliptin / metformin FDC, as part of the Adverse Reactions – Postmarketing Experience section.

On October 12<sup>th</sup>, 2007 DMEP approved a Prior Approval Supplement (PAS) labeling requesting addition of the following information to labeling of these two products, as summarized in the Highlights section of the sitagliptin label:

“There have been postmarketing reports of serious allergic and hypersensitivity reactions in patients treated with JANUVIA such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. In such cases, promptly stop JANUVIA, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes. (5.3, 6.2)”

Among the case reports submitted with the PAS supplement in 2007, it is conceivable that those reports describing cutaneous hypersensitivity where possible cases of cutaneous vasculitis. The applicant considers the terms cutaneous vasculitis, hypersensitivity vasculitis and leukocytoclastic vasculitis interchangeable for the purpose of the present CBE supplement.

### **2.1 Cutaneous vasculitis**

A brief synopsis on cutaneous vasculitis is presented in this section to provide context to aid in the proper interpretation of the applicant and OSE’s postmarketing findings. The synopsis is based on the chapter entitled “Cutaneous Vasculitis” written recently by Ibrahim and Nousari and used as a

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reference by the applicant<sup>1</sup>.

Vasculitis is defined as inflammation of blood vessel walls. It results in wall destruction and increased permeability, which can lead to aneurysm formation, extravasation of blood cells, and stenosis. Clinically, these processes present as hemorrhage, tissue ischemia, or infarction of the affected organ. Depending on the organs and caliber of blood vessels involved, vasculitis can manifest with a wide spectrum of clinical findings - from a benign, self-limiting course, to death. Vasculitis can be a primary process (idiopathic) or a secondary manifestation of other triggers such as trauma, infection, malignancy, systemic inflammatory conditions, connective tissue disease, and drug hypersensitivity. The skin is one of the most common organs affected by vasculitis.

The annual incidence of biopsy-confirmed cutaneous vasculitis has been reported from 40 to 60 cases per million. Approximately 30% to 60% of vasculitides limited to the skin are idiopathic without evidence of extracutaneous involvement and with no obvious trigger. These cases are typically solitary, self-limited episodes, although as many as 10% of these patients may have recurrent or chronic disease. Of the remaining patients, 20% are attributable to adverse drug reactions, 22% to infection, 12% to connective tissue disease, 10% to Henoch- Schönlein purpura, and less than 5% each to malignancy, systemic vasculitis, or other systemic disease.

Medications from virtually every pharmacologic class (including herbal supplements) have been linked to drug-induced vasculitis, resulting in a range of clinical presentations. The onset of findings after exposure to the causative agent is typically 5 to 20 days, and while withdrawal is often sufficient to reverse the vasculitic process, there have been cases of fatal drug-induced allergic vasculitis in previously healthy patients. There have also been reports of cutaneous vasculitis stemming from vaccines, foods, and alcohol.

Classification of vasculitis in the skin is typically based on the size of predominantly affected blood vessels and type of inflammatory responses.

*Reviewer comment: The applicant proposes to add the term cutaneous vasculitis to labeling. In the applicant's discussion, the term cutaneous vasculitis is equivalent to leukocytoclastic vasculitis and hypersensitivity vasculitis. So, in this review I focused on the information about leukocytoclastic vasculitis in the reference used.*

### Cutaneous Leukocytoclastic Vasculitis

Exogenous chemicals, infectious agents, cytokines, and circulating immune entities that do not strongly activate complement can cause leukocytoclastic vasculitis by inducing an inflammatory cascade in endothelium of the cutaneous small vessels. Most commonly triggered by infections or drugs, the onset is acute with both palpable and non-palpable purpuric and urticarial lesions on the lower extremities appearing 5 to 20 days after initial exposure, and 2 to 4 days after repeat exposures. These cases tend to be single episodes, and relapsing cycles can result from systemic inflammatory conditions, infection, and malignancy. Extracutaneous involvement is rare, with the exception of constitutional symptoms caused by mediators of inflammation released locally.

Routine laboratory tests are usually normal. The erythrocyte sedimentation rate is elevated in up to 50% of cases, while complement levels and urinalysis are normal. There are no specific serologic markers for leukocytoclastic vasculitis, making it largely a diagnosis of exclusion, and urticarial vasculitis with normal complement is likely to be a clinical variant of this condition. On histology,

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<sup>1</sup> Ibrahim SF, Nousari CH. Cutaneous vasculitis, a chapter in "Clinical and Basic Immunodermatology" Editors: Gaspari AA and Tyring SK, Publisher Springer London 2009.

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there is a neutrophil predominant vasculitis of superficial vessels with varying numbers of surrounding eosinophils. Direct immunofluorescence is positive in roughly half of these biopsies, displaying mild to moderately intense granular IgM deposits with weak or absent C3. The lack of complement involvement may correlate with the relatively benign course of this condition and low level of systemic involvement. Although direct immunofluorescence is frequently negative, it is a key factor in discriminating leukocytoclastic vasculitis from IgA vasculitis, which shares the same triggers and clinical presentation. Up to half of the cases of leukocytoclastic vasculitis are idiopathic and resolve spontaneously. In cases with a known trigger, treatment consists of removal of the offending agent or resolution of underlying systemic condition. Immunosuppressive treatment is largely unnecessary in leukocytoclastic vasculitis, with the exception of the most severe cases, and is aimed at reducing constitutional symptoms and synovitis. Moderately dosed corticosteroids (0.5 mg / kg / day) are a reasonable option until symptoms resolve. Recalcitrant cases warrant more extensive investigation.

## **3. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY**

### **3.1 Sources of Clinical Data**

The review described in this document is based on the data submitted by the applicant in the CBE labeling supplement, data from the OSE consultation, and the recommendations from OSE.

### **3.2 Review Strategy**

In this review, the data submitted by Merck in the CBE supplement are reviewed first, followed by a review of the OSE consultation memorandum.

## **4. INTEGRATED REVIEW OF SAFETY**

### **4.1 Methods and Findings**

#### **4.1.1 Pre-clinical and Clinical Trial Experience**

No signal for vasculitis has been noted in the pre-clinical development of sitagliptin. The main issue related to the toxicity of DPP4 inhibitors relates to the specificity of inhibition of DPP4 over other dipeptidyl peptidases. At the time of the original review of the sitagliptin NDA, five other compounds in this class tested in monkeys had been associated with dose and duration-dependent necrotic skin lesions (tail, digits, ears, nose, and scrotum). Two of these 5 also produce lesions in dogs (footpad sores, edema, limping) and one produces lesions in rats and monkeys.

The applicant has demonstrated that sitagliptin is a potent, selective DPP4 inhibitor based upon in vitro (human, mouse, rat and dog serum) and in vivo animal pharmacology studies. Importantly, sitagliptin is a highly selective over DPP8/9 (>2500-fold); inhibition of these enzymes has been previously demonstrated to result in marked toxicity in preclinical species. The sitagliptin 3-month toxicity study conducted in monkeys (the most sensitive species) was unrevealing, whereas another

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less potent and less specific compound tested concurrently by Merck revealed similar skin toxicities, renal toxicities and death.

The applicant received two postmarketing reports of cutaneous vasculitis from clinical studies.

### 4.1.2 Postmarketing Experience

#### Merck's CBE supplement data

The international date of launch of sitagliptin was August 4<sup>th</sup>, 2006 and of sitagliptin / metformin FDC was March 30<sup>th</sup>, 2007. A search of WAES or Adverse Reactions (ARs) covering the period from the international approval of these products through February 3<sup>rd</sup>, 2009 was conducted by the applicant. The search used the following MedDRA terms: "cutaneous vasculitis", "leukocytoclastic vasculitis", "perivascular dermatitis", "vasculitis", "vasculitic rash" and "vascular skin disorder". A total of 15 reports (13 spontaneous, 2 clinical study) were received: six were for leukocytoclastic vasculitis, five for vasculitis and one for each of the other terms searched. Eight of the 15 reports met the regulatory criteria for a serious report; 7 reports were non-serious. Of the 15 reports, 13 were received for sitagliptin and 2 for sitagliptin / metformin FDC. All 15 reports were received from healthcare providers. Two of the 15 reports described a diagnosis of leukocytoclastic vasculitis confirmed by skin biopsy.

The 15 reports were received from 4 countries, United States (8), France (3), Germany (3) and the Philippines (1). Information regarding age was provided in 11 / 15 (73 %) reports, median age was 64 years old (range 45 to 88 years of age). Information regarding gender was provided in 14 / 15 (93%) reports: 6 / 15 were in females and 8 / 15 reports were in males. Time to onset was provided in 9 / 15 (60%) report, ranging approximately 8 days to approximately 244 days, median 43 days. Information regarding outcome and action taken with regard to sitagliptin or sitagliptin / metformin FDC was provided in 12 of 15 (80%) reports; 8 patients were reported as recovered or recovering and 4 patients were reported as not recovered.

The reports are summarized below:

- **VASCULAR SKIN DISORDER:** Information has been received from a physician concerning an 88-year old male patient from France with osteoarthritis, cardiac failure, hypertension, prostatic adenoma, hyperuricemia, left renal cyst and pacemaker generated rhythm. For non-insulin-dependent diabetes mellitus, he was placed on therapy with metformin tablet, 700 mg daily and acarbose. On 4/29/08, therapy with acarbose was discontinued and switched to therapy with sitagliptin tablet, 100 mg, once a day for non-insulin-dependent diabetes mellitus. Concomitant therapy included furosemide, digoxin, telmisartan, dutasteride, acenocoumarol, allopurinol, trimetazidine, pantoprazole, zolpidem and tiotropium. On [REDACTED] (b) (6), the patient was hospitalized for renal insufficiency (creatinine = 24 mg/L) with inflammatory syndrome (C-reactive protein = 175 mg/L), anemia (hemoglobin = 8.7 g/L) and general physical health deterioration. Temperature was normal. During hospitalization, serum glucose tests showed a trend to hypoglycemia for which therapy with metformin was discontinued. Hypoglycemia resolved. The patient received 3 red cell packs. On [REDACTED] (b) (6), general physical health deterioration and renal insufficiency were resolved (creatinine = 16 mg/L), inflammatory syndrome and CRP increase were resolving (35 mg/L) and anemia outcome was unknown. The patient was discharged from hospital. No explanation for the renal insufficiency, inflammatory syndrome with C-reactive protein increase, anemia and general physical health deterioration

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was found. The physician reported that the patient might have taken without medical prescription non steroid anti-inflammatory therapy that could explain the renal insufficiency. On 6/10/08, the patient experienced vein insufficiency (left leg) with start of skin trophic disorder. On 6/30/08, therapy with sitagliptin was discontinued. At the time of the present report (6/30/08), the patient's vein insufficiency with skin trophic disorder persisted. The reporter felt that vein insufficiency with skin trophic disorder might be related to therapy with sitagliptin. She felt that hypoglycemia was related to therapy with metformin and/or sitagliptin. She felt that renal insufficiency, inflammatory syndrome, C-reactive protein increase, anemia and general physical health deterioration were not related to therapy with sitagliptin. Additional information has been requested.

- **PERIVASCULAR DERMATITIS:** WAES 0806USA07839 Initial and follow-up information has been received from a physician concerning a 66 year old white female retired registered nurse who on 8/14/07 was placed on therapy with sitagliptin phosphate 100 mg, once a day for the treatment of type 2 diabetes mellitus. No new medications were started since sitagliptin. After seven months (also reported as a "couple months") of taking therapy with sitagliptin, in April 2008, the patient developed a macular / reticular rash, asymptomatic (no pruritus or pain or swelling) on her knees, over a period of weeks progressed to involve her legs excluding feet. Lower part of abdomen was also involved. On 5/13/08, biopsy was performed on one specimen consisting of a 3 mm skin punch biopsy measuring 3 mm deep. Microscopic description: "Sections show skin and underlying subcutaneous tissue. The skin surface is unremarkable. The dermis shows a mild perivascular chronic lymphocytic infiltrate intermixed with mast cells. No vasculitis is seen. The changes observed may be seen in various conditions including allergic reaction vs. urticarial reaction." Skin biopsy diagnosis: Superficial and deep perivascular chronic dermatitis.
- **CUTANEOUS VASCULITIS:** WAES 0803PHL00012 described a 72 year old, male Asian patient with hypertension, cardiovascular disorder, dyslipidemia and a history of drug hypersensitivity on therapy with other medications who was placed on sitagliptin 100mg daily for approximately 5-6 months and concomitant atorvastatin calcium, clopidogrel bisulfate, furosemide, voglibose, glipizide, perindopril, and metformin. He experienced rashes and itchiness in the arms and thighs, which later developed into lesions. One week later he experienced skin vasculitis accompanied by edema and was reportedly hospitalized due to edema, although it was unknown whether this was due to his other concurrent cardiovascular conditions or due to suspect therapy. He was treated with cetirizine and fexofenadine. Therapy with sitagliptin was discontinued during his hospitalization. He recovered from skin vasculitis and edema. While the role of sitagliptin in this event cannot be totally excluded, assessment of this report is confounded by concomitant medications associated with cutaneous vasculitis.
- **VASCULITIS:** WAES 0706USA02738 Information has been received from a physician concerning a 64-year old male who was placed on therapy with sitagliptin phosphate 100 mg, once a day for glycemic control (duration not reported). The physician reported the patient had taken sitagliptin and he experienced a non-pruritic, generalized skin rash with vasculitis. He was hospitalized and treated with intravenous steroids. The physician considered the non-pruritic, generalized skin rash with vasculitis Other Important Medical Events as they required intervention to prevent serious criteria.
- **VASCULITIC RASH:** WAES 0708USA03369 Information has been received from a physician concerning a female in her "upper" seventies who was placed on therapy with sitagliptin phosphate, tablet for the treatment of diabetes (dose and duration not reported). In (b) (6)

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the patient experienced a vasculitis-like rash and was hospitalized. Therapy with sitagliptin phosphate was discontinued. As of (b) (6) the patient was still hospitalized and was recovering. No further information is available as the physician did not wish to be contacted.

- VASCULITIS: WAES 0710USA03977 described a patient (gender not reported) on sitagliptin and concomitant etanercept as well as other unspecified therapies who subsequently developed vasculitis (time to onset was not reported) and was hospitalized. The reporting physician attributed the vasculitis to etanercept (indication NR). Cutaneous vasculitis is a labeled adverse event for etanercept.
- VASCULITIS: 2 non-serious reports (WAES 0802USA04440, 0708USA02340) provided limited information for assessment. The remaining report (WAES 0809USA03916) described a female patient in her late 40's with no pertinent medical history who was placed on therapy with sitagliptin 100 mg, once a day for the treatment of borderline type 2 diabetes mellitus. There was no concomitant medication. After approximately 7 weeks, she reportedly developed vasculitis with a red, swollen face and lower extremity edema. Therapy with sitagliptin was discontinued and the patient recovered.

Six reports of leukocytoclastic vasculitis were received (3 serious, including 1 positive rechallenge, and 3 non-serious). Of the 6 reports, 4 reports (WAES 0901DEU00031, 0811DEU00013, 0802DEU00045, 0809FRA00032) either provide insufficient information to suggest more than a temporal association between the AR and treatment with sitagliptin or are confounded by concomitant medications that include cutaneous vasculitis in the prescribing information (e.g., amlodipine, atorvastatin, HCTZ, simvastatin, valsartan).

The remaining 2 serious reports described a diagnosis of leukocytoclastic vasculitis confirmed by skin biopsy and are summarized below:

- One report described an inadvertent positive rechallenge (WAES 0711USA00326). This report described a 59 year old male enrolled in a clinical trial for approximately 4.5 months when he received treatment with nystatin cream for tinea cruris. Two days later the patient was admitted to the hospital for a severe allergic reaction with urticarial vasculitis, balanoposthitis and staphylococcus aureus bacteriuria with normal urinalysis and absence of urinary symptoms after receiving blinded therapy for approximately 19 weeks and nystatin cream for 2 days. At that time the acute allergic reaction was felt to be related to nystatin cream applied topically to a rash on the penis and scrotum. Concomitant medications included insulin, lisinopril and pravastatin. The patient was treated with promethazine HCL, meperidine HCL, IV ciprofloxacin, vancomycin and dexamethasone. Infectious Disease and Urology were consulted. Urology recommended local care with povidone-iodine irrigation and soak, and Silvadene cream for the balanoposthitis. The Infectious Disease consultant noted the patient had a methicillin-sensitive Staphylococcus aureus bacteriuria and recommended discontinuation of IV antibiotics and treatment with oral cephalexin. Subsequently, the patient was discharged to home on cephalexin, sulfamethoxazole (+) trimethoprim, prednisone taper, acetaminophen (+) hydrocodone bitartrate, diphenhydramine and local genital care. The patient was instructed to discontinue study medication; however, the patient restarted study medication on his own. He had taken the study medication for approximately 4 days when he was re-hospitalized with an infection of the foreskin of his penis with an abscess, and the investigator also noted that patient had hives. Treatment included rifampin, loratadine, and diphenhydramine HCL. Study

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medication was discontinued. During the second hospitalization, debridement of penile abscess and circumcision was performed and the patient was discharged to home the following day. Upon discharge, the sub-investigator confirmed the presence of diffuse urticarial rash. Dermatology was consulted and a biopsy diagnosed urticarial vasculitis (leukocytoclastic vasculitis) with significant eosinophilic infiltration suggestive of a drug reaction. Forty-five days after discontinuing therapy with sitagliptin, the patient recovered. Study drug was unblinded; the patient was treated with sitagliptin 100 mg daily.

- The remaining serious report of leukocytoclastic vasculitis (WAES 0811FRA00050) described a 55-year old female with dyslipidaemia, hypertension, morbid obesity, metabolic syndrome and microalbuminuria who was placed on therapy with sitagliptin tablet, 100 mg once a day for insulin-requiring type 2 diabetes mellitus. Concomitant therapy included insulin, atorvastatin, gliclazide, metformin (+) pioglitazone, hydrochlorothiazide (+) irbesartan, trimetazidine and metformin. Approximately 14 days after sitagliptin initiation, the patient experienced papulo-erythematous lesions, very pruriginous, very infiltrated, located on the ankles (2 lesions) and on the feet (2 lesions). There were no systemic symptoms or evidence of infection. Sitagliptin was discontinued and the patient was hospitalized. Skin biopsy revealed "lymphocytic vasculitis, maybe sequelae to leukocytoclastic vasculitis, with C3, IgA, IgM and slight IgG deposition. Capillaries were surrounded with lymphocytes cuff. On some sections, there was fibrinoid necrosis in blood vessel walls meaning vasculitis lesions with few picnotic nucleus that could be sequellar to leukocytoclastic nuclear dust. The infiltrate was essentially made of lymphocytes with very rare eosinophils. CH50 was increased (154 - unit not reported) in consistency with inflammatory syndrome. Native deoxyribonucleic acid, antinuclear antibodies, auto-antibodies were negative." The patient subsequently experienced 2 new lesions on the thighs with pseudo-urticaria aspect and was placed on topical corticoids. Approximately 2 weeks later the lesions resolved. Final dermatological diagnosis was toxicoderma with allergic vasculitis. The reporter felt that toxicoderma with allergic vasculitis was related to therapy with sitagliptin.

## Merck's analyses

### Estimation of reporting rate

Since market introduction for each product to 1/31/09, the worldwide distribution of sitagliptin and sitagliptin/metformin FDC is (b) (4) tablets and (b) (4) tablets, respectively. The patient exposure for sitagliptin is estimated to be (b) (4) patient-years based on the assumption of 1 tablet per day and (b) (4) patient years for sitagliptin / metformin FDC based on 2 tablets per day. Based on drug distribution figures for both drugs (b) (4) the estimated reporting rate for cutaneous vasculitis is 0.0005% or 5 per million person-years.

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## Data from OSE consultation

The strategy used by OSE to search AERS was as follows:

- Drug names: Januvia, sitagliptin phosphate, Janumet, sitagliptin/metformin, including combination products
- Drug role: Suspect
- AERS Outcome: All
- MedDRA Terms: Standardized MedDRA Query (SMQ) broad- Vasculitis, Version 11.1, which includes the following Preferred Terms (PT):  
Allergic granulomatous angiitis, anti-neutrophil cytoplasmic antibody positive vasculitis, aortitis, arteritis, arteritis coronary, arteritis obliterans, Behcet's syndrome, capillaritis, cerebral arteritis, Cogan's syndrome, cutaneous vasculitis, diffuse vasculitis, erythema induratum, erythema nodosum leprosum, Henoch-Schonlein purpura, injection site vasculitis, Kawasaki's disease, Langerhans' cell granulomatosis, leukocytoclastic vasculitis, lupus vasculitis, Majocchi's purpura, microscopic polyangiitis, nodular vasculitis, ocular vasculitis, polyarteritis nodosa, polymyalgia rheumatica, pseudovasculitis, pulmonary vasculitis, renal arteritis, retinal vasculitis, rheumatoid vasculitis, Schamberg's disease, segmented hyalinizing vasculitis, Takayasu's arteritis, temporal arteritis, thromboangiitis obliterans, vascular purpura, vasculitic rash, vasculitis, vasculitis cerebral, vasculitis gastrointestinal, vasculitis necrotizing, viral vasculitis, Wegener's granulomatosis, antibody test abnormal, antibody test positive, antineutrophil cytoplasmic antibody increased, antineutrophil cytoplasmic antibody positive, blood viscosity increased, cryoglobulinemia, cryoglobulins present, Goodpasture's syndrome, palpable purpura, plasma viscosity abnormal.
- Search Date: From U.S. approval date for each drug (Januvia October 16, 2006 and Janumet March 20, 2007) through May 20, 2009.

The following criteria were used to select cases:

- Clinical diagnosis of vasculitis, AND
- Temporal association with sitagliptin use and the vasculitis event.

Search through AERS yielded 17 reports of vasculitis associated with use of sitagliptin. Three reports were excluded from analysis because of duplication, miscoded event, and no temporal relationship (one report for each of these reasons).

Of the 14 cases remaining, 9 were from the U.S. and 5 were foreign cases. Two cases reported the use of the combination product Janumet and 4 cases reported concomitant use of metformin. The two cases where sitagliptin / metformin FDC was suspected reported leukocytoclastic vasculitis (1) and polymyalgia rheumatica (1). Please refer to Table 1.

There were 11 cases where skin is involved: 5 leukocytoclastic vasculitis of skin, 1 Schamberg's disease (no vasculitis reported), and 5 vasculitis skin rash of various body parts. There were two cases of polymyalgia rheumatica (one of upper arms and legs, one unspecified; no further testing on vasculitis reported). One case did not specify the site of vasculitis. Three cases also reported edema besides skin rash. No case reported severe systemic vasculitis involving multiple organs. However, 5 U.S. cases and 4 foreign cases reported hospitalizations due to vasculitis events.

Skin biopsy was used to confirm diagnosis in three leukocytoclastic vasculitis cases. Only one case reported negative findings of antinuclear antibodies. No case reported finding of the biomarker

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antineutrophil cytoplasm antibody that is sometimes associated with drug-induced vasculitis.

**Table 1. Demographic and clinical characteristics of cases of vasculitis reports in AERS received from October 16, 2006 to May 20th, 2009**

Selected characteristics	Cutaneous vasculitis N = 11	Other vasculitis N = 3	Cumulative Vasculitis N = 14
Age (years)	N = 8	N = 2	N = 10
Range	45 – 75	42 – 78	42 – 78
Median	62	60	62
Gender	Male 4 Female 6 Unknown 1	Male 2 Female 0 Unknown 1	Male 6 Female 6 Unknown 2
Outcome	Hospitalization 7 Other 3	Hospitalization 2 Disability 1	Hospitalization 9 Other 3 Disability 1
Time to onset (days)	N= 6	N = 2	N =8
Range	1 – 120	15 – 60	1 - 120
Median	21	37.5	21
Challenges	N=11	N=3	N=14
Positive Dechallenge	6	2	8
Negative Dechallenge	1	0	1
Unreported outcome	4	1	5
Diagnosis confirmed by biopsy	3	0	3
Treatment with steroids	2	1	3

Table adapted from the OSE consultation memo

One case of positive rechallenge reported among the applicant's WAES search results was missed in the OSE AERS search: WAES 0711USA00326. In that case the patient re-initiated treatment with sitagliptin on his own and had recurrent skin lesions.

## OSE's analyses

OSE reported the utilization data for sitagliptin and sitagliptin / metformin FDC but did not report the reporting rate.

A temporal relationship is observed in this case series. Three cases specified that there were no concomitant medications. One case reported autoimmune disease in medical history and one case reported concurrent unspecified infection that may impede in the differential diagnosis of drug-induced vasculitis from the primary cause. The rest of 12 cases did not report these two alternative etiologies (autoimmune disease and concurrent infection).

Eleven cases in this case series are cutaneous in nature. Of the three non-cutaneous cases, one did not specify the site involved; two reported polymyalgia rheumatica (one domestic and one foreign) and had limited information to ascertain the vessels affected and the association with sitagliptin therapy. Although both cases reported symptoms resolved after discontinuation of sitagliptin therapy, no other diagnostic tests or rationale was mentioned in the reports. The evidence presented in these two cases is very limited with regards to establishing a causal association with exposure to sitagliptin.

## OSE's recommendations:

- Modify the labeling to include cutaneous vasculitis in the postmarketing adverse reaction section.
- OSE will continue to monitor all types of vasculitis.

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## **5. OVERALL ASSESSMENT**

### **5.1 Conclusions**

Most of the postmarketing reports of cutaneous vasculitis founds in AERS or submitted by the applicant in support of this CBE supplement lack important information to ascertain the correct diagnosis. In addition, diabetes is a complex disease, and patients are treated simultaneously with multiple drugs, many of which can be suspects in triggering episodes of cutaneous or hypersensitivity vasculitis.

It is difficult from these cases to estimate correctly a reporting rate. It is also difficult to accurately estimate a background rate for comparison and to assess whether sitagliptin treatment may increase the risk of cutaneous vasculitis.

In a few of the cases reported, biopsy-proven leukocytoclastic vasculitis temporally associated with the treatment with sitagliptin has been documented.

With these considerations, I consider beneficial to inform health care providers about the potential risk of cutaneous vasculitis through a change in labeling.

### **5.2 Recommendation on Regulatory Action**

I recommend approval of the language proposed by the applicant, specifically, to add the term “cutaneous vasculitis” under the Adverse Reactions – Postmarketing Experience section of the sitagliptin and the sitagliptin / metformin FDC labels.

### **5.3 Recommendation on Postmarketing Actions**

- None.

### **5.4 Labeling Review**

I recommend approving the changes being effected to the package insert, as proposed by the applicant, Merck.

### **5.5 Comments to Applicant**

None.

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## **6. APPENDICES**

### **6.1 Line-by-Line Labeling Review**

Not applicable.

### **6.2 Other Pertinent Information**

Not applicable.

## **REFERENCES**

1. Ibrahim SF, Nousari CH. Cutaneous vasculitis, a chapter in “Clinical and Basic Immunodermatology” Editors: Gaspari AA and Tyring SK, Publisher Springer London 2009.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 21995	SUPPL 13		JANUVIA 100MG (SITAGLIPTIN PHOSPHATE)
NDA 21995	SUPPL 13		JANUVIA 100MG (SITAGLIPTIN PHOSPHATE)

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/s/  
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ILAN IRONY

08/08/2009

This is a review of cutaneous vasculitis in the CBE supplement. A review of pancreatitis is filed under a separate review

MARY H PARKS

08/18/2009

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**CLINICAL REVIEW**

Application Type: NDA

Submission Number: 21995 and 22044

Submission Code: Labeling Supplement CBE

Letter Date: 2009-03-05

Stamp Date: 2009-03-05

PDUFA Goal Date: 2009-09-05

Reviewer Name: Ilan Irony

Through: Mary Parks

Review Completion Date: 2009-08-06

Established Name: Sitagliptin Phosphate

Sitagliptin / metformin fixed-dose combination

Trade Name: Januvia and Janumet

Therapeutic Class: Dipeptidyl Peptidase IV inhibitor

Dipeptidyl peptidase IV inhibitor / biguanide

Applicant: Merck

Priority Designation: S

Formulation: Tablets

Dosing Regimen: 25 mg, 50 mg and 100 mg once daily for Januvia

50 mg / 500 mg and 50 mg /1000 mg twice daily for Janumet

Indication: Improvement in glycemic control

Intended Population: Type 2 diabetes mellitus

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# 1. EXECUTIVE SUMMARY

Sitagliptin is a member of a new class of anti-diabetic drug products called dipeptidyl peptidase IV (DPP4) inhibitors, approved in the United States in October 2006 for the treatment of type 2 diabetes mellitus. Sitagliptin / metformin as a fixed dose combination (FDC) was approved in March 2007.

Through these two supplemental NDAs (sNDAs), the applicant requests a change in product labeling (changes being effected, or CBE) based on post-marketing observations of cases of pancreatitis and various forms of cutaneous vasculitis. The applicant requests that these adverse reactions be added to the label under Section 6.2 “Postmarketing Experience”.

Similar corresponding changes are requested for the Patient Package Insert. This review document will address the post-marketing reports of pancreatitis and the medical officer’s recommendations for labeling of sitagliptin and sitagliptin / metformin FDC. The cases of cutaneous vasculitis included in this CBE supplement are reviewed in a separate review document.

## 1.1 Recommendation on Regulatory Action

I recommend approval of the CBE supplement as proposed by the applicant. The term “pancreatitis” should be added as adverse reaction (AR) to Section 6.2 “Postmarketing Experience”. My recommendation is based on the review of data submitted by the applicant, consults received from the Division of Pharmacovigilance I (DPV I) and from the Division of Epidemiology (DEPI), both under the Office of Surveillance and Epidemiology (OSE) / CDER, and after internal discussions within our Division and between our Division and OSE.

In a search of its Worldwide Adverse Events System (WAES), Merck noted postmarketing reports of pancreatitis in patients treated with sitagliptin or with sitagliptin / metformin FDC. These reports prompted the submission of this CBE supplement. Merck noted that the reporting rate was below that of background, the incidence of pancreatitis in a diabetic population not exposed to sitagliptin. Our Division consulted with OSE for an interrogation of FDA’s Adverse Event Reporting System (AERS) regarding this potential unlabeled risk and for an estimate of the reporting rates of pancreatitis associated with sitagliptin and with sitagliptin / metformin FDC. The emphasis of the OSE consult was the rare, but more severe complicated cases of acute pancreatitis, namely the necrotizing and / or hemorrhagic forms. Although the primary safety evaluator and the primary epidemiology reviewer reached different recommendations as to the appropriate section in labeling for placement of the adverse reaction, the OSE leadership recommended including “pancreatitis” under Warnings and Precautions. OSE based their recommendation on two factors:

- The reporting rates of pancreatitis with sitagliptin may be similar to those reported with exenatide (the latter had the label amended to add a Warning and Precaution against the risk of hemorrhagic or necrotizing pancreatitis), although the reporting rates with sitagliptin could be lower than those with exenatide depending on the analysis conducted;
- A possible plausible mechanism was reported in an animal model of Type 2 diabetes mellitus (T2DM) treated with sitagliptin, in which pancreatic ductal metaplasia and pancreatitis were reported.

The following issues informed my recommendation:

- Even if the background rate of pancreatitis among diabetics is overestimated by one third, as

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argued by OSE, the “true” background rate is still the same or slightly above the reporting rate with sitagliptin or sitagliptin / metformin FDC.

- The proportion of complicated forms of pancreatitis with sitagliptin is the same or lower than the proportion reported in the general population or in the diabetic population.
- The rat model that served as a basis for a plausible mechanism for the increased risk of pancreatitis is intriguing, but more toxicology studies are needed to confirm the applicability of the model to the majority of patients with T2DM.

## 1.2 Recommendation on Postmarketing Actions

I recommend that the applicant conduct a pharmacology animal study as well as a clinical trial to further explore the potential mechanisms for increased risk of acute pancreatitis and complicated forms of pancreatitis associated with the use of sitagliptin.

## 1.3 Summary of Clinical Findings

### 1.3.1 Merck’s data

Merck searched its WAES for reports containing the terms “pancreatitis”, “acute pancreatitis”, “blood amylase increased”, “blood lipase increased” and “hyperlipasemia” associated with sitagliptin or sitagliptin / metformin FDC, from the worldwide market introduction of these products until February 3, 2009. The worldwide market introduction for sitagliptin was August 4<sup>th</sup>, 2006 and for sitagliptin / metformin FDC was March 30<sup>th</sup>, 2007. The search yielded 142 reports. Of these, 34 cases appeared only due to enzyme elevation and lacked other clinical data. Thus, 108 cases captured the terms “pancreatitis” or “acute pancreatitis”. Eighty four percent of these 108 cases were from the United States. Information on age was provided in 68 of the 108 reports. The median age was 64 years (range: 36 to 88 years). Gender information was provided in 93/108 reports: 41/93 (44%) reports concerned females. Approximate time to onset was provided in 51/108 (47%) reports, with a median 56 days (range: 1 to 682 days). Median time to recovery after discontinuing sitagliptin or sitagliptin/metformin FDC was 7 days (range: 1 to 51 days) in the 17 reports containing this information. Of the 108 reports, 38 contained insufficient information to allow a full assessment of the cases. Other 52 reports contained sufficient information but “the diagnosis was not confirmed by imaging findings”. Two thirds of the 52 reports were confounded by use of concomitant medications that list pancreatitis as AR in their label and / or concurrent illness or past medical history consistent with increased risk for pancreatitis. Among these 52 reports, there were 2 deaths listing pancreatitis (one of these deaths was at least partly due to hemorrhagic pancreatitis). The remaining 18 reports of the 108 had clinical diagnoses and imaging: 3 cases recovered from pancreatitis while still on sitagliptin, 5 cases were confounded, 2 cases had CT findings of chronic pancreatitis, one case had imaging consistent with chronic pancreatitis and deformed anatomy and was confounded by medications, one case had pancreatitis due to pancreatic cancer and another had imaging consistent with pancreatic mass and inflammation prior to sitagliptin treatment. The remaining 5 reports had sufficient information to allow full assessment and no other apparent confounders: one of these was a case of necrotizing pancreatitis while treated with both metformin and sitagliptin.

Merck’s analysis of reporting rate includes all 142 reports in the numerator and assumed a total worldwide exposure of (b) (4) patient-years (sales data for sitagliptin and sitagliptin / metformin FDC combined) as the denominator. Thus, Merck’s calculated reporting rate is 0.005% or

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approximately 50 cases per million person-years of exposure. Merck compared this rate to the yearly incidence rate reported among placebo-treated diabetic subjects in the FIELD study (a 5-year study of fenofibrate therapy in 9795 diabetics) of 0.094%. Merck admits to the fact underreporting of pancreatitis to WAES may have occurred, and the magnitude of the underreporting is difficult to estimate.

### 1.3.2 OSE data

OSE searched the AERS database based on terms almost identical to Merck's search of their WAES system. OSE found 131 cases. The cases were reviewed and selected if they either contained a diagnosis of acute pancreatitis, or they met two of the three following criteria:

- a) Severe and sudden midepigastric abdominal pain,
- b) Increased serum amylase (normal 30-170 U/L) and / or lipase (normal 7-60 U/L)
- c) Confirmatory diagnostic imaging results (including ultrasound, computed tomography, or other imaging techniques).

Upon application of the selection criteria, 88 cases remained. The demographic characteristics, time from sitagliptin initiation to the event reported, and proportion of confounded cases was very similar to Merck's. OSE's memo mentioned 2 cases of necrotizing pancreatitis. In the estimation of reporting rate of pancreatitis, OSE used 68 unique domestic cases as the numerator and 969,131 person-years exposure in the US as the denominator, yielding a reporting rate of 70 cases per million-person years, a very similar reporting rate as estimated by Merck, which had used worldwide data for both numerator and denominator. OSE compared this reporting rate with that reported for other antidiabetic drugs. While lower than exenatide, the rate associated with sitagliptin was higher than metformin, glimepiride, nateglinide or pramlintide. In another comparison against other drugs, the rate of complicated pancreatitis (1 per million person-years) was substantially lower than that for exenatide (18 per million person-years), but higher than pramlintide (0). OSE estimated the background rate of acute pancreatitis not triggered by alcohol use or gallstones, which resulted in hospitalization, to be 123 per million person-years, but questioned whether the true rate is lower by 1/3 (after exclusion of chronic pancreatitis as the diagnosis at discharge); still the reporting rate of sitagliptin-associated pancreatitis according to OSE estimates is lower than the background rate in the general population. Since diabetics have a higher incidence of pancreatitis than the general population, the rate of sitagliptin-associated pancreatitis is lower than that in the non-exposed diabetic population.

Due to the serious nature of the disease, and the fact that a minority of these cases were complicated cases, the OSE leadership recommended conveying information about the risk of pancreatitis, including hemorrhagic or necrotizing pancreatitis, under the Warnings and Precautions in the sitagliptin and sitagliptin / metformin FDC labeling. In support of this decision, the OSE reviewer and the DPV I Division Director alluded to an animal model of T2DM treated with sitagliptin which has demonstrated histopathologic findings of pancreatic ductal metaplasia and pancreatitis (three of eight animals), including one of eight animals with hemorrhagic pancreatitis. Dr. Brinker, a team leader in Epidemiology in OSE, reviewed the reporting rate of sitagliptin as compared to that of exenatide, instead of a comparison to background. In his analysis, Dr. Brinker censored the cases of pancreatitis with exenatide after December 31<sup>st</sup>, 2006, due to the fear that many cases after that date were due to stimulated reporting (i.e., notoriety of the pair exenatide – pancreatitis due to FDA alert, lay press, etc). He included 31 cases of pancreatitis which were reported through 6 quarters of marketing with sitagliptin and 30 cases which were reported with exenatide through a

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similar duration, but from launch to 12/2006. Although the numerator (number of cases of pancreatitis) is nearly identical, the exposure to sitagliptin was twice that of exenatide (the denominator). Dr. Brinker concludes that a factor of 2 is insufficient to discriminate the relative risks of exenatide versus sitagliptin, and similar regulatory actions must be entertained for the two. Merck has also shown an analysis of sitagliptin-associated pancreatitis reporting over time, and has seen, similar to exenatide, evidence for stimulated reporting after August 2008, likely due to a perceived similarity between the drugs from the perspective of the health care provider (HCP), due to similar mechanism of glycemic action (both have effects based on increased GLP-1 activity). If a similar approach to censor cases reported after August 2008 were to be taken for sitagliptin-associated pancreatitis, the relative risk of sitagliptin would have been even lower than half of the risk with exenatide.

### 1.3.3 Drug-Drug Interactions

The manuscript published by Dr. Butler's group<sup>1</sup>, on which OSE relies partly to justify the decision to add the pancreatitis risk to the Warnings and Precautions section, concludes with the following: "An intriguing finding in the current study is the fact that addition of metformin to sitagliptin prevented the sitagliptin-mediated increase in ductal replication. Because metformin therapy has been shown to increase GLP-1 levels in some studies, the action to counter sitagliptin-mediated increased ductal replication is presumably independent of GLP-1. It is possible that the effect was mediated indirectly through metabolic actions of metformin to enhance insulin sensitivity or decrease blood glucose concentrations. Alternatively, metformin might act directly on ductal cells to suppress proliferation." It is noteworthy that pancreatitis cases were reported both in patients taking sitagliptin as well as in patients taking sitagliptin and sitagliptin / metformin FDC (with approximately the same proportions given the different exposures to these two) and that the complicated cases (hemorrhagic or necrotizing pancreatitis) occurred in patients also treated with either of these drugs. Even though some of the reports do not list all antidiabetic drugs taken at the time of pancreatitis onset, a number of patients were taking metformin concomitantly with sitagliptin.

## 2. INTRODUCTION AND BACKGROUND

Exenatide was approved in the U.S. in April of 2005, as a treatment for T2DM. Exenatide (tradename Byetta) exerts its glycemic effect as a glucagon-like peptide 1 (GLP-1) agonist. Unlike GLP-1, exenatide is resistant to inactivation by dipeptidyl peptidase IV (DPP4). The clinical trials conducted prior to approval have not demonstrated evidence of increased risk of pancreatitis. In October 2007 FDA has issued a safety alert regarding the increased risk of pancreatitis associated with exenatide. A second safety alert for exenatide has been issued in August 2008, in order to inform HCP and the public about the cases of hemorrhagic or necrotizing pancreatitis, including fatalities. In addition, sponsors of other GLP-1 agonists under investigation have sent expedited safety reports to FDA regarding serious cases of pancreatitis. Sitagliptin was approved in the U.S. on October 16<sup>th</sup> 2006, as the first drug in the DPP4 inhibitor class, under the tradename Januvia. On March 30<sup>th</sup>, 2007 the fixed dose combination of sitagliptin

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<sup>1</sup> Matveyenko AV, Dry S, Cox HI et al. Beneficial Endocrine but Adverse Exocrine Effects of Sitagliptin in the Human Islet Amyloid Polypeptide Transgenic Rat Model of Type 2 Diabetes. Interactions with Metformin. Diabetes 58: 1604-1615, 2009.

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and metformin was approved in the US, under the tradename Janumet. DPP4 inhibition improves glycemic control in patients with T2DM due to prolongation of the half-life of endogenous GLP-1, as well as the half life of another DPP4 substrate, glucose-dependent insulinotropic polypeptide. Although exenatide has a different mechanism to enhance the GLP-1 effect, both exenatide and the DPP4 inhibitors are considered incretin-based treatments.

I have received sporadic expedited 15-day reports regarding pancreatitis from AERS under NDA 21995 (sitagliptin) and NDA 22044 (sitagliptin / metformin FDC) for these two drugs and line listings of pancreatitis submitted with the Periodic Safety Update Reports from Merck. After the first safety alert was issued for exenatide, I have requested an informal consultation in December 2007 to the safety evaluator in OSE for an AERS search for cases of pancreatitis and acute pancreatitis with the use of sitagliptin and sitagliptin / metformin FDC. That search followed by data mining yielded a conclusion that there was no signal of pancreatitis with either drug, with a low EB05 score (EB05 is the lower limit of the 95 % CI for the Empirical Bayes Geometric Mean (EBGM); EBGM is an adjusted estimate for the ratio of observed to expected counts and its value indicates the strength of the reporting relationship between a particular drug and adverse event). Please refer to Table 1.

**Table 1. Results of AERS data mining for sitagliptin and pancreatitis as conducted in December 2007**

Event	N	EBGM	EB05	EB95
acute pancreatitis	5	1.391	0.662	2.65
pancreatitis	17	0.826	0.549	1.2

In view of the safety alerts related to exenatide, and after Merck's submission of the CBE on March 5<sup>th</sup>, 2009, DMEP requested a formal consult to the Division of Pharmacovigilance I in OSE on March 11, 2009.

Around the same time, DMEP was made aware of an electronic publication of a manuscript authored by Dr. Peter Butler and his group in the journal Diabetes, which described the effect of sitagliptin, or sitagliptin combined with metformin, on the endocrine and exocrine function of the pancreas in a particular species of Sprague-Dawley rat, the human islet amyloid polypeptide (IAPP) transgenic (HIP). The manuscript concluded that, while the endocrine effects on glycemia were similar to those found in other efficacy models in T2DM studied by Merck and by sponsors of other DPP4 inhibitors under development, a 12-week exposure to sitagliptin lead to pancreatic ductal metaplasia, with some of the treated animals having pathologic evidence of pancreatitis and one animal having hemorrhagic pancreatitis.

This review document will cover Merck's CBE supplement data with subsequent data communicated by the applicant in response to DMEP's questions, as well as comments to the reviews from OSE and to the Butler paper.

## **3. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY**

### **3.1 Sources of Clinical Data**

This review is based on Merck's CBE supplement for the cases reported to WAES and the drug

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utilization data provided by the applicant, as well as the consult to OSE regarding the risks of pancreatitis with exenatide and with sitagliptin. The few Journal publications consulted are listed under References, at the end of this review document.

## 3.2 Review Strategy

In this review, the data submitted by Merck in the CBE supplement are reviewed first, followed by a review of the OSE consultation memoranda. Cases of hemorrhagic and / or necrotizing pancreatitis are referred to as complicated pancreatitis, in contrast with acute pancreatitis, which are also known as edematous pancreatitis. Associations between sitagliptin or sitagliptin / metformin FDC in the description of cases of complicated pancreatitis reported are highlighted in **bold and red** type.

## 4. INTEGRATED REVIEW OF SAFETY

### 4.1 Methods and Findings

#### 4.1.1 Pre-clinical and Clinical Trial Experience

There has been no evidence of pancreatitis in the extensive pre-clinical toxicology testing conducted by Merck in multiple animal species (mice, rats, dogs and monkeys). Toxicology studies were not conducted, however, in animal models of the disease. This is the usual approach in the pre-clinical development of antidiabetic products.

In a pooled analysis of safety in over 6000 subjects from 12 Phase II / III studies of up to 2 years in duration, the incidence rates of adverse events (AEs) of pancreatitis in the sitagliptin and control (non-exposed) groups were: pancreatitis (0.1% [2 / 3415] and 0%, respectively) and acute pancreatitis (0% and 0.1% [2 / 2724], respectively). Two of these Phase III studies subsequently continued (P036-10 and P052 Phase B), and an additional subject in the sitagliptin-exposed group (P036-10) was reported to have an event of acute pancreatitis associated with a concomitant triglyceride level of 3249 mg/dL. Since this analysis, an additional 5 Phase III randomized controlled clinical studies (P047, P049, P051, P064, and P079 Phase A) have undergone database lock with subsequent unblinding. In these studies, none out of 1843 subjects in the sitagliptin groups and 1 out of 1832 subjects in the non-exposed groups was reported to have an AE of pancreatitis (P079): this event was reported as acute pancreatitis occurring in a subject receiving metformin 2000 mg/day.

For the recently approved saxagliptin, the second drug in the DPP4 inhibitor class, no excess cases of pancreatitis were reported in the saxagliptin-treated subjects, compared to the non-exposed population. As of the cutoff date for the 120-day safety update, there were 6 / 3356 (0.2%) saxagliptin-treated subjects and 2 / 1251 (0.2%) comparator-treated subjects (both receiving metformin) in the phase II / III program with events that coded to the MedDRA preferred terms for pancreatitis, acute pancreatitis, or chronic pancreatitis. There were no AEs coded to preferred terms for abnormal serum amylase or lipase.

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### 4.1.2 Postmarketing Experience

#### Merck's CBE supplement data

In the WAES database search, Merck employed the terms “pancreatitis”, “acute pancreatitis”, “blood amylase increased”, “lipase increased” and “hyperlipasemia” in patients on therapy with sitagliptin or sitagliptin / metformin FDC from the date of their worldwide market introduction through February 3<sup>rd</sup>, 2009. The worldwide market introduction for sitagliptin was August 4<sup>th</sup>, 2006 and for sitagliptin / metformin FDC was March 30<sup>th</sup>, 2007. There were 142 spontaneous reports describing 147 patients: 108 reports (106 from HCP, 2 from consumers) mapping to pancreatitis (87 reports) / acute pancreatitis (21 reports) and 34 reports (33 HCP, 1 consumer) mapping to blood amylase increased, lipase increased and hyperlipasemia.

Merck did not describe the 34 reports which were based on enzyme elevation alone, citing paucity of information, presence of confounding factors, and lack of confirmatory imaging tests provided in the reports. After a subsequent query by DMEP, Merck provided further information that 15 of the 34 patients also had some abdominal symptoms (predominantly pain, but also distension and indigestion). However, in the analysis of incidence rates, Merck has used 142 reports as the numerator.

From the 108 reports with clinical information (please refer to Figure 1)

Ninety one of the 108 reports of pancreatitis were received from the U.S. (84%). Information on age was provided in 68 / 108 (63%) reports. The median age was 64 years (range 36 to 88 years). Information regarding gender was provided in 93 / 108 (86%) reports: 41 / 93 (44%) reports concerned females and 52 / 93 (56%) reports concerned males. Approximate time to onset was provided in 51 / 108 (47%) reports and ranged from 1 to approximately 682 days, with a median of 56 days. Time to recovery after discontinuing sitagliptin or sitagliptin/metformin FDC was provided in 17 / 108 (16%) reports and ranged from 1 day to 51 days, with a median of 7 days.

Thirty-eight of the 108 (35%) reports provided insufficient information to allow for full assessment.

Fifty-two (48%) reports provided some information on history, concomitant medications or clinical course but did not confirm the diagnosis of pancreatitis by imaging studies.

*Reviewer comment: Imaging studies are not required for confirmation of the diagnosis of pancreatitis: the typical presentation allows for a clinical diagnosis based on past medical history, physical findings, and elevation of amylase and / or lipase. Imaging sometimes does not allow adequate distinction between acute pancreatitis and chronic pancreatitis, particularly when symptoms suggestive of an acute exacerbation manifest in the setting of the latter. On the other hand, imaging is necessary to document necrotizing or hemorrhagic forms of pancreatitis, since the severity of the clinical presentation, Ranson's criteria or degree of enzyme elevation may not be indicative of these outcomes.)*

Of these 52 reports, approximately two-thirds were confounded by concomitant medications that include pancreatitis in the prescribing information (atorvastatin, rosuvastatin, simvastatin, amlodipine and ACE-inhibitors) and / or concurrent illnesses / past medical history predisposing to

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pancreatitis (gallstones, alcohol use / abuse, pre-existing history of pancreatitis, and pancreatic cancer). After a subsequent query by DMEP, Merck provided further clarification that 21 of these 52 (40%) reports provided information regarding abdominal pain. Twenty of the 52 reports (38%) provided information regarding elevation of pancreatic enzymes; 13 of these 20 reports (65%) provided laboratory values, and 12/20 (60%) of the reports which provided information on laboratory values also noted the patients experienced abdominal pain.

Among these 52 reports were 2 reports of fatalities (one with hemorrhagic pancreatitis), described below:

- WAES 0709USA04017 (PSUR # 3) described a 68-year old Hispanic male with coronary artery disease, hyperlipidemia, hypertension, peripheral vascular disorder, and allergic rhinitis on therapy with **sitagliptin** 100 mg daily (duration not reported) and concomitant irbesartan hydrochlorothiazide, atorvastatin, montelukast, metoprolol XL and clonidine. The patient developed actinomycosis presenting as indurated nodules on his arms and legs. Bone marrow biopsy performed was suggestive of lymphoma. No diagnostic studies were provided. Subsequently the patient died. Causes of death were listed as pancreatitis, skin abscesses to leg (possible Stevens-Johnson syndrome). The action take with sitagliptin was not provided in the report. The reporting physician felt pancreatitis was not related to sitagliptin since the patient had many medical problems including actinomycosis, “early lymphoma” and acute renal failure. Additional information received from a line listing obtained by Merck from the FDA under the Freedom of Information Act after the cutoff date of February 3<sup>rd</sup>, 2009 noted the patient’s autopsy showed **hemorrhagic pancreatitis**. Merck subsequently requested additional information; however, further information was not obtained.
- WAES 0811USA03765, follow-up received after 03-Feb-2009, described pancreatitis (no diagnostic/laboratory tests provided) in a schizophrenic 75-year old male with COPD, CAD, hyperthyroidism, sleep apnea and diverticulitis in a nursing home on sitagliptin (dose and duration not reported). Concomitant medications (also reported as “a lot”) included levothyroxine, alprazolam, pioglitazone, carvedilol, and aspirin. Sitagliptin was discontinued and the pancreatitis continued. Subsequently, the patient died. The death was attributed to “other complications” (unspecified). The physician reported it did not appear pancreatitis was related to the use of sitagliptin.

Eighteen reports were cases of pancreatitis/acute pancreatitis confirmed by imaging studies:

- 3 reports noted recovery while continuing therapy with sitagliptin.
- 5 reports were confounded by concomitant medications possibly associated with pancreatitis (statins, ACE-inhibitors, amlodipine, fenofibrate, hydrochlorothiazide, acetaminophen, and montelukast) but provided no start/stop dates to allow for full assessment.
- 2 reports noted CT findings consistent with chronic pancreatitis.
- 1 report attributed pancreatitis to pancreatic cancer.
- 1 report noted a pre-existing pancreatic mass and inflammation of the pancreas.
- 1 report described acute pancreatitis with MRI findings of pancreatic atrophy with mild to moderate dilatation of the pancreatic duct in an 84-year old white female with multiple concurrent conditions/history (including COPD, Barrett’s esophagus, hypercholesterolemia, vitamin B12 deficiency, GERD, and history of cholecystectomy). Medications included sitagliptin 100 mg daily (duration approximately 3 months) and 28 other medications, which included atorvastatin, repaglinide, and fenofibrate. Initial lipase was 1991 U/L. A gastrointestinal consultant questioned whether acute pancreatitis could have been related to

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sitagliptin or “just an exacerbation of chronic underlying pancreatitis due to distorted anatomy”. Sitagliptin was discontinued with intravenous fluid administration and gradual reintroduction of a diet. The patient was discharged after 5 days with fluctuating lipase levels, iron deficiency anemia and “elevated cancer antigen 19-9 of 72”. One week later, the patient was readmitted with recurrence of pain and lipase of 1073 U/L. Subsequently, the patient was discharged home with lipase still elevated (285 U/L at discharge) but decreasing to 207 U/L over the next month.

Despite some limitations with the reported data, the remaining 5 reports describe a temporal association between the use of sitagliptin or sitagliptin/metformin FDC and pancreatitis in which causality cannot be ruled out. One of these 5 reports was a case of “possible” necrotizing pancreatitis in the setting of sitagliptin / metformin FDC, as summarized below:

- Report WAES 0810DEU00004 described a diagnosis of acute pancreatitis in a patient with CT evidence of inflammation of the duodenum, “most likely caused by the passage of an obstruction” with subsequent radiographic impression of **possible necrotizing pancreatitis**. This report concerns a 50-year old female with obesity, hyperlipidemia, HTN, and hypothyroidism on **sitagliptin/metformin FDC 50/1000 mg** twice daily initiated on August 25<sup>th</sup>, 2008. Concomitant medications included amlodipine, enalapril, levothyroxine, metformin and metoprolol. It was reported the patient was hospitalized (date NR) and lipase was 138 U/L and amylase 30 U/L. No further information was provided and the patient was discharged on (b) (6). On September 9<sup>th</sup>, 2008, the patient experienced exhaustion and weakness and sitagliptin/metformin FDC was discontinued. On (b) (6) the patient was re-hospitalized with nausea, vomiting, and acute upper abdominal pain, lipase 15,416 U/L, amylase 238 U/L, WBC 11,600 mcrL and normal transaminase. The patient was treated in the ICU from (b) (6) with metoclopramide, butylscopolamine, proton pump inhibitors and piritramide. All other medications continued except for sitagliptin (metformin restarted September 9<sup>th</sup>, 2008). On (b) (6) ultrasound revealed steatosis hepatitis and no gallstones. Ultrasound on (b) (6) revealed atonic gallbladder and no stones. On (b) (6) abdominal CT scan showed an enlarged inflammatory conglomerate in transition area between pancreatic corpus and head, including duodenum and infiltration in liver hilus and a large pseudocyst. Necroses were seen until caudal area reaching caudal pole of the kidney. Hepatic steatosis was confirmed, and gallbladder was well defined without inflammatory process. Stomach was dilated including inflammation of the duodenum. Subsequently, the patient improved. Repeat ultrasound (b) (6) showed a 5 cm echo-poor space occupying lesion in transition area between pancreatic corpus and head, possibly corresponding to a cystic lesion in the context of a necrotizing pancreatitis.

A case of necrotizing pancreatitis associated with the use of sitagliptin was received by Merck after the February 3<sup>rd</sup>, 2009 cutoff date. The report is summarized as follows:

- Report WAES 0906FRA00083 (initial report received March 9<sup>th</sup> 2009 and follow-up received on July 10<sup>th</sup>, 2009) described a 59-year old male with history of pancreas divisum, hypertension, hypercholesterolemia and diabetic nephropathy with no history of alcoholism. On January 27<sup>th</sup>, 2009, the patient was placed on therapy with **sitagliptin 100 mg** daily for diabetes and on amlodipine. Concomitant therapy included metformin, glimepiride, atorvastatin and perindopril. He was hospitalized on (b) (6) for **necrotizing pancreatitis**. Therapy with sitagliptin

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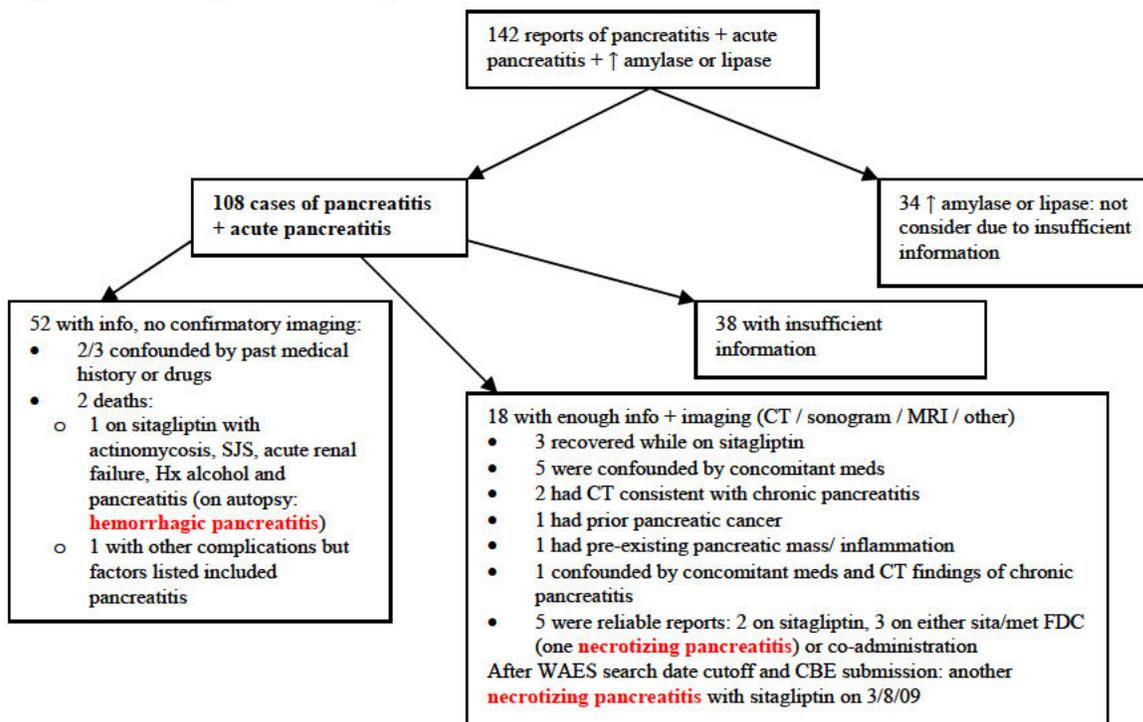
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was discontinued. Biliary magnetic resonance imaging showed pancreas divisum. CT scan showed necrotizing pancreatitis. Hepatic and biliary ultrasound was normal (no lithiasis). Necrotizing pancreatitis resolved slowly. No further information is expected.

Another case of necrotizing pancreatitis was associated with the use of sitagliptin / metformin FDC. The case is summarized as follows:

- WAES 0903USA02872, received from a line listing obtained on request by the Company from the FDA under the Freedom of Information Act, described a 43-year old non-smoker male who had been lost to medical follow up for 2-3 years, and who 5 years prior was taking atorvastatin with good lipid control but then stopped with no follow up laboratory values available. On January 1<sup>st</sup>, 2007, the patient was placed on therapy with **sitagliptin / metformin FDC 50 mg / 500 mg** tablet for T2DM. The patient was reported to be on no concomitant medication. On January 19<sup>th</sup>, 2009, the patient presented with diabetes ketoacidosis, acute **necrotizing pancreatitis** and acute necrotizing esophagitis. Pancreatitis was thought to be secondary to hypertriglyceridemia (triglycerides 1950 [units not provided] on admission). CT scan of the abdomen and pelvis showed less than 30% of the pancreas remaining. The physician stated that the patient had mistakenly taken sitagliptin / metformin 4 times per day for an extended period of time until August 2008. It was unclear from the pharmacy whether he was receiving medication amounts that would allow such frequent dosing. Therapy with sitagliptin / metformin FDC was discontinued on January 19<sup>th</sup>, 2009. On the same day the following laboratory results (units not specified) were obtained: sodium 118; chloride 62; potassium 4.5; CO<sub>2</sub> 12.9; glucose 1010; BUN 137; creatinine 3.6; lipase 167. The original reporting source was a physician.

Figure 1. Summary flowchart of pancreatitis cases in Merck's WAES



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In response to one of DMEP's queries, Merck provided updated information included in the latest PSUR covering the period February 4<sup>th</sup> 2009 through June 30<sup>th</sup>, 2009. The information for pancreatitis is summarized in Table 2 and Table 3:

**Table 2. JANUVIA Marketed Reports of Pancreatitis ADRs Reported per PSUR Period**

	Pancreatitis (Pancreatitis/Acute Pancreatitis)	Pancreatitis Hemorrhagic	Pancreatitis necrotizing	Total Reports Pancreatitis ADRs	Total Tablets (period exposure)	Patient yrs. (period exposure)
PSUR # 1 8/5/06 to 2/3/07	4 (2/2)	0	0	4		(b) (4)
PSUR # 2 2/4/07 to 8/3/07	12 (10/2)	0	0	12		
PSUR # 3 8/4/07 to 2/3/08	16 (13/3)	0	0	16		
PSUR # 4 2/4/08 to 8/3/08	24 (21/3)	0	0	24		
PSUR # 5 8/4/08 to 2/3/09	38 (30/8)	0	0	38		
2/4/09 to 6/30/09	23 (3/20)	1*	1	25		
TOTAL 8/4/06 to 6/30/09	117	1*	1	119		

\* WAES 0709USA04017 changed from Pancreatitis in PSUR #3 to hemorrhagic pancreatitis upon f/u from FDA FOI after data lock of PSUR #5.

**Table 3. JANUMET Marketed reports of Pancreatitis ADRs Reported per PSUR Period**

	Pancreatitis (Pancreatitis/Acute Pancreatitis)	Pancreatitis Hemorrhagic	Pancreatitis necrotizing	Total Reports Pancreatitis ADRs	Total Tablets (period exposure)	Patient yrs. (period exposure)
PSUR # 1 3/30/07 to 9/29/07	1 (1/0)	0	0	1		(b) (4)
PSUR # 2 9/30/07 to 3/29/08	2 (1/1)	0	0	2		
PSUR # 3 3/30/08 to 9/29/08	4 (3/1)	0	0	4		
PSUR # 4* 7/16/08 to 2/3/09	7** (6/1)	0	0	7		
2/4/09 to 6/30/09	16 (16/0)	0	1	17		
TOTAL 3/30/07 to 6/30/09	30 (27/3)	0	1	31		

\* Timeframe of PSUR # 4 changed due to EMEA request of simultaneous submission of Januvia and Janumet PSURs.

\*\*Includes 1 report (WAES 0810DEU00004) of possible necrotizing pancreatitis noted on CT scan but not reported as having a diagnosis of necrotizing pancreatitis.

DMEP questioned Merck about the timing of the reporting of these ARs, to evaluate the potential for stimulated reporting of pancreatitis associated with sitagliptin or sitagliptin / metformin FDC based on the safety alerts issued by FDA for exenatide. Reports of pancreatitis associated with

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exenatide have clearly demonstrated stimulated reporting. The particular timepoints of interest to DMEP for investigation on possible stimulated reporting of pancreatitis associated with sitagliptin were October 2007, January 2008 and August 2008.

In Merck's reply, the initial date of the report received by Merck was the date considered for the timeline. Figure 2 and Figure 3 depict the timeline of sitagliptin and sitagliptin / metformin FDC reports, respectively, of pancreatitis/acute pancreatitis received by month and year. As seen in Figure 2, the cumulative number of reports of pancreatitis/acute pancreatitis for sitagliptin from market introduction was 23 through October 2007, 32 through January 2008 and 65 through August 2008. The data reveal that there is an increase in number of reports in relation to these dates. Similarly as seen in Figure 2, there is an increase in the number of sitagliptin/metformin FDC reports of pancreatitis/acute pancreatitis received after August 2008 (Figure 3). This pattern suggests stimulated reporting for sitagliptin and sitagliptin / metformin FDC temporally related to FDA Alerts on pancreatitis with exenatide.

**Figure 2. JANUVIA: Number of Adverse Experience Reports of Pancreatitis / Acute Pancreatitis Received by Month and Year (Total N = 94)**

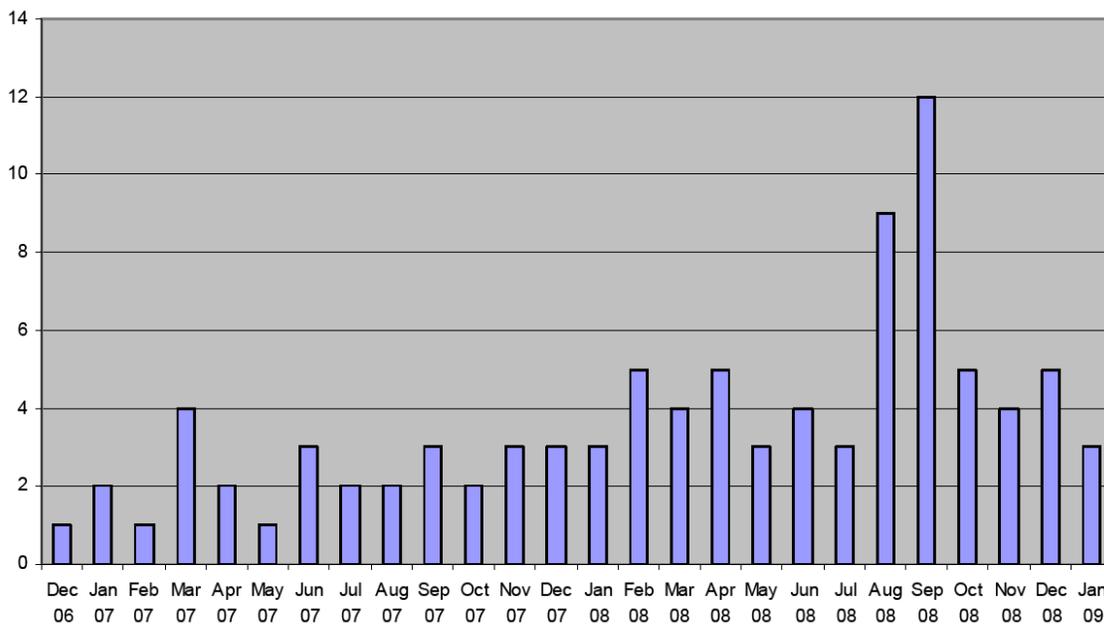


Figure copied from the applicant's response to DMEP query.

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**Figure 3. JANUMET: Number of Adverse Experience Reports of Pancreatitis / Acute Pancreatitis Received by Month and Year (Total N = 14)**

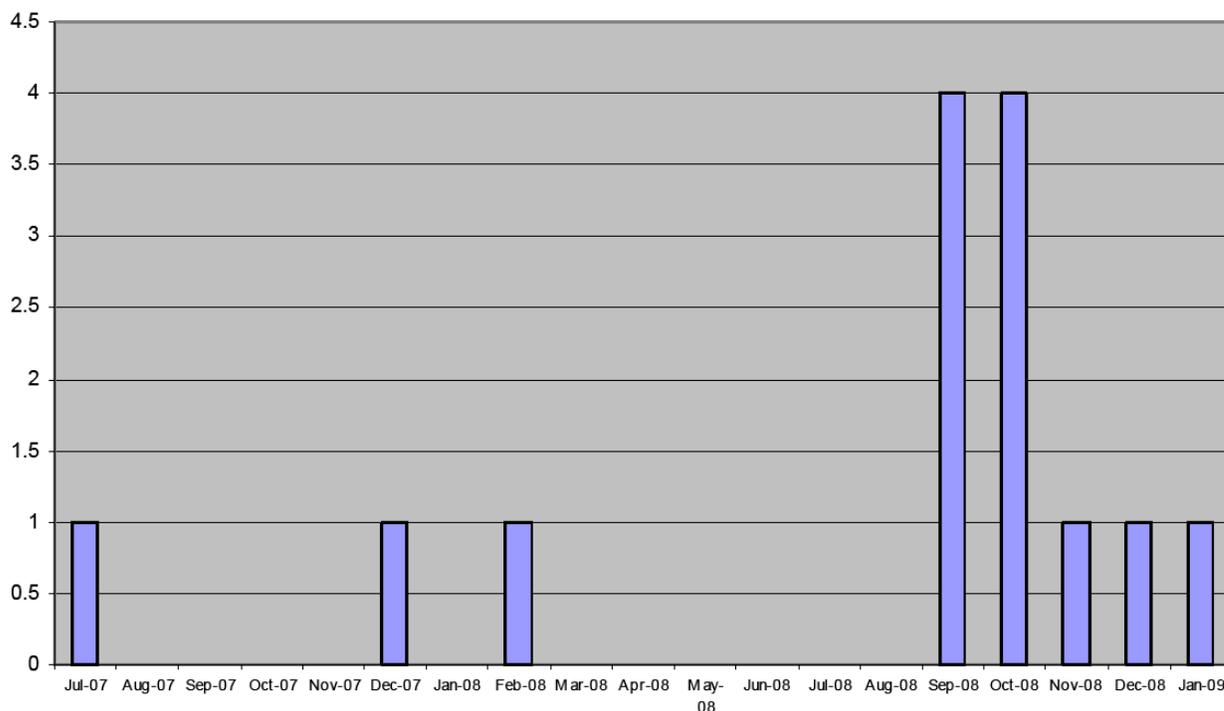


Figure copied from the applicant's response to DMEP query.

## Merck's analyses

### Analysis of the background rate of pancreatitis in the diabetic population

The age-standardized incidence of acute pancreatitis in the U.S. population is reported in the range of 0.033% to 0.044% per year, based on an epidemiologic study conducted in California from 1994 to 2001. The cumulative incidence of acute pancreatitis in patients with T2DM from the placebo arm in the FIELD study was 0.47% (23 / 4900 subjects) over a 5-year period. The FIELD study was a trial to evaluate the long-term effect of fenofibrate on cardiovascular events among 9795 subjects with T2DM who were randomized 1:1 to receive fenofibrate or placebo. Conversion of the FIELD study data to a crude yearly incidence rate of pancreatitis in T2DM would be approximately 0.094%.

A case-control study conducted by the Medical Product Agency in Sweden estimated that the crude odds ratio (95% CI) of 1.9 (1.2, 3.1) for acute pancreatitis for patients with T2DM relative to those without T2DM among patients hospitalized with new onset pancreatitis. In a recently published paper in *Diabetes Care*<sup>2</sup> based on a retrospective analysis of a proprietary claims database, the incidence of acute pancreatitis in patients was estimated to be 422 cases per 100,000 patient-years, which was 2.83 times the rate estimated for the non-diabetic general cohort in the same database (149 cases per 100,000 patient-years). That paper was supported by Amylin and Lilly (the manufacturers of exenatide) and was submitted for publication in September 2008 (after the FDA's second safety alert), so some caution is necessary in interpreting these data. However, the data are

<sup>2</sup> Noel RA, Braun DK, Patterson RE, Bloomgren G. Increased risk of Acute Pancreatitis and Biliary Disease Observed in Patients with Type 2 Diabetes: a Retrospective, Cohort Study. *Diabetes Care* 32(5): 834-8, 2009.

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compatible with the Swedish data summarized above, and it is plausible that patients with T2DM, with an expected higher mean triglyceride levels, and higher rates of obesity and gallstones, would have a higher incidence of pancreatitis compared to the non-diabetic population. The correct estimation of the background rate of pancreatitis is an important issue, as the reporting rates of pancreatitis for these products (exenatide, sitagliptin or sitagliptin / metformin FDC) are compared to the background rates of pancreatitis, for an observed-to-expected analysis.

### Analysis of drug utilization (exposure to sitagliptin and sitagliptin / metformin FDC)

Since market introduction for each product to January 31<sup>st</sup>, 2009, the **worldwide** distribution of sitagliptin and sitagliptin / metformin FDC is (b) (4) tablets and (b) (4) tablets, respectively. The patient exposure for sitagliptin is estimated to be (b) (4) patient-years based on the assumption of 1 tablet per day and (b) (4) patient years for sitagliptin/metformin FDC based on 2 tablets per day. Based on drug distribution figures for both drugs (b) (4), the estimated **worldwide** reporting rate for pancreatitis, including pancreatic enzyme abnormalities, is 0.005%.

### Observed-to-expected analysis

The estimated reporting rate (0.005%) of pancreatitis in patients treated with sitagliptin, and sitagliptin / metformin FDC is below the estimated cumulative incidence of acute pancreatitis in patients with T2DM from the placebo arm in the FIELD study. Based on the currently available information, the number of observed cases of pancreatitis in patients exposed to sitagliptin and sitagliptin / metformin FDC does not appear to exceed the known background rate in the patient population. However, it is unclear if the actual number of reports of pancreatitis in patients exposed to sitagliptin or sitagliptin / metformin FDC is higher than the observed cases reported in the WAES database due to under-reporting in the postmarketing environment.

Merck concludes that: "Although it is difficult to prove cause and effect from spontaneous reports, based upon the review of these reports of pancreatitis, and after taking into account any potential underlying conditions and concomitant medications which may be associated with this kind of adverse event, as well as the potential of increased risk of pancreatitis in the diabetic population, a causal relationship between pancreatitis and the use of sitagliptin or sitagliptin/metformin FDC appears unlikely but cannot be definitively excluded."

### Data from OSE consultation

The strategy used by OSE to search AERS was as follows:

- Drug names: Januvia, sitagliptin phosphate, Janumet, sitagliptin/metformin, including combination products
- Drug role: Suspect
- AERS Outcome: All
- MedDRA Terms:
- High Level Term- Acute and Chronic Pancreatitis and
- Preferred Term- Blood Amylase or Lipase Increased, Pancreatic Enzymes Increased
- Search Date: From U.S. approval date for each drug (Januvia October 16, 2006 and Janumet

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March 20, 2007) through February 9, 2009.

The following criteria were used to select cases:

- Clinical diagnosis of acute pancreatitis, OR
- If the case report had no mention of clinical diagnosis of acute pancreatitis but had two of the three following criteria (a plus b or c), the case was determined to be “acute pancreatitis”
  - a) Severe and sudden midepigastic abdominal pain,
  - b) Increased serum amylase (normal 30-170 U/L) and/or lipase (normal 7-60 U/L),
  - c) Confirmatory diagnostic imaging results [including ultrasound, computed tomography (CT), or other imaging techniques]
- All cases must be temporally associated with sitagliptin use and the pancreatitis event.

Of 131 reports found in AERS, 43 were excluded upon review due to a number of factors, the two most common being:

- An alternative explanation exists in the report (n= 17)
- Did not meet the selection criteria (n = 16)

Of the 88 cases remaining, 11 were treated with sitagliptin / metformin FDC and 22 were treated with sitagliptin and metformin coadministered. The demographic and clinical characteristics of these cases were similar to those in Merck’s WAES:

The age range for 54 of the reports was 36 to 88 years (median 62 years); of 72 cases with gender information, 31 were female; 69 of the 88 reports were domestic; of 21 reports with information on hospitalization, the range was 1 to 32 days (median 5); of 48 with time from initiation of treatment to onset of pancreatitis, the range was 2 to 300 days (median 60 days); there were 47 positive dechallenges (defined as the partial or complete disappearance of an adverse event after withdrawal of the drug); 6 cases with negative dechallenge, in which sitagliptin was discontinued at the time of onset (with 3 of these with outcome not resolved at the time of reporting and 3 with unknown outcome); there were no cases of positive rechallenge and one case with negative re-challenge.

Of the 88 cases, 31 had signs or symptoms: of these 29 had abdominal pain and 15 had nausea and vomiting; median amylase (NR 30 – 170 U/L) was 300 U/L (range 75 to 1900) among 14 cases in whom an amylase result was reported; median lipase (NR: 7 – 60 U/L) was 236 U/L (range 54 – 15416 among 27 cases in whom a lipase result was reported; and about 50 % had risk factors (co-medications, confounding conditions, or both).

The 2 cases of necrotizing pancreatitis associated with sitagliptin / metformin FDC reported by Merck in the CBE supplement were also identified by OSE through the AERS search.

## **OSE’s analyses**

Dr. Yinghua Wang, the safety reviewer from OSE, notes that approximately 25% of all attacks of pancreatitis are acute and severe in nature leading to complications and an estimated 9% of mortality. Her statement (based on a surgical textbook<sup>3</sup> referenced) confirms that patients with pancreatitis may present for medical attention with a wide spectrum of severity and, at the time of presentation, they may have manifested the more complicated forms of necrotizing and / or hemorrhagic pancreatitis.

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<sup>3</sup> Schwartz’s Principles of Surgery –8th Ed. (2005) – Online. Chapter 32: Pancreas.

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*Reviewer comment: one of the arguments made by OSE that a public health benefit of adding “pancreatitis” as a Warning and Precaution” in labeling is that by stopping the injuring factor (presumably sitagliptin), a HCP may be able to stop progression from the milder edematous pancreatitis to the complicated form. This argument cannot be confirmed by medical experience and by the surgical reference used in the OSE’s own review. In addition, I note that the proportion of complicated pancreatitis reported in the literature is at least the same, and likely higher (10 – 20 %), than the proportion of complicated cases in this sitagliptin and sitagliptin / metformin FDC series (granted that the number of cases [3] is very small for a robust conclusion).*

Based on the review of AERS data, Dr. Wang concludes that “these cases suggest that sitagliptin exposure may increase the risk of pancreatitis, either through a direct effect on the pancreas or pancreatic duct outflow system, or indirectly by affecting another risk factor (e.g. effects on gallbladder motility, serum triglyceride levels, etc.). In addition, animal data showed evidence that sitagliptin may exert effects on the exocrine pancreas in conjunction with its known insulinotropic effects. High rates of pancreatic duct cell turnover and ductal metaplasia have been observed in sitagliptin-treated rats, suggesting yet undefined pleiotropic effects of sitagliptin and possibly other members of the drug class on pancreatic exocrine physiology.”

*Reviewer comment: The review of AERS data merely shows that a number of patients developed pancreatitis after initiation of treatment with sitagliptin. One cannot conclude, based on these data, that the risk is increased due to exposure to sitagliptin. The causality association comes from speculation about a potential mechanism, and reliance on an animal model which may or may not be an adequate representation of the majority of diabetics.*

### Analysis of drug utilization (exposure to sitagliptin and sitagliptin / metformin FDC)

For the purpose of the analysis of reporting rates, OSE considered the 68 unique cases reported from the U.S. as the numerator. OSE’s next task in determining the reporting rate for sitagliptin was the estimation of exposure, or drug utilization. Data on drug utilization for this review was extracted from the Wolters Kluwer Source Pharmaceutical Audit Suite Prescription Monthly database, for the period 2005 through 2008, in the U.S. market. OSE estimated that the combined exposure for sitagliptin and sitagliptin / metformin FDC was (b) (4) person-years (the denominator). Therefore the reporting rate of pancreatitis for the combined sitagliptin and sitagliptin / metformin FDC was estimated at 70 cases per million person-years, or 0.007%.

*Reviewer comment: This reporting rate, estimated by OSE, based on domestic case reports of pancreatitis and on U.S. exposure to these drugs, is very similar to the reporting rate calculated by Merck, with a different adjudication criterion for worldwide cases to be included in the numerator, and for a worldwide exposure as the denominator.*

OSE then provided two comparisons for the estimated reporting rate of pancreatitis associated with the use of sitagliptin: against the estimated background rate of pancreatitis in the general population (observed-to-expected analysis) and against other antidiabetic drugs in current use in the U.S. (drug-against-drug analysis).

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### Observed-to-expected analysis

Assuming the background rate is 123 cases of pancreatitis per million person-years, one may conclude that exenatide stands just above the background rate and sitagliptin stands below the background rate. OSE put into question the accuracy of the background rate, stating that the figure may overestimate the true rate by as much as one third, because the rate includes also hospital discharges listing chronic pancreatitis as the diagnosis. Dr. Wang comments in her review that, since we may need to count a case of chronic pancreatitis which flares upon exposure to sitagliptin with regards to estimating the numerator for the reporting rate, we must not discard the cases of chronic pancreatitis which are hospitalized and are not related to known etiologies such as alcohol use or gallstones in the process of estimating the denominator.

### Drug-against-drug analysis

The OSE-estimated reporting rate of pancreatitis for exenatide was 144 per million person-years as of July 12<sup>th</sup>, 2007, prior to the FDA alert to HCP and the increased media scrutiny, to avoid the stimulated reporting that inevitably followed. Exenatide is a reasonable comparator, in view of the common incretin-base effect, distinct from any prior approved classes of antidiabetic drugs. Exenatide also had a much higher reporting rate of complicated pancreatitis, compared to sitagliptin (12 U.S. cases for exenatide against three for sitagliptin worldwide) despite the higher exposure to the latter. In addition to exenatide, OSE used other commonly used antidiabetic drugs as comparators, and found the reporting rate for metformin to be 3.6 per million person-years and for glimepiride to be 10 per million person-years.

The regulatory decision taken recently for exenatide, after extensive discussion between the Office of New Drugs and OSE, was to add pancreatitis under the Warnings and Precautions in the label. I support that decision for the following three reasons:

- The estimated rate of pancreatitis was above the background rate, suggesting a possible relationship, albeit not strong based simply on the reporting rate against background;
  - There seems to be a class effect with other GLP-1 agonists also being associated with pancreatitis, sometimes a few hours after injection in normal volunteers without risk factors
- With the greater absolute number of cases of complicated (i.e., hemorrhagic or necrotizing) pancreatitis compared to sitagliptin or other antidiabetic drugs, and the stronger association as evidence in the prior 2 bullets, there is merit in including the risk of pancreatitis where it draws more attention from HCP and patients (through the use of a Medication Guide), and it may prevent re-exposure to exenatide in a patient with prior history of exenatide-associated edematous pancreatitis to recur into a complicated case.

On the other hand, the reporting rate for sitagliptin was lower than the background rate (even if the background was reduced by 1/3 to 81 cases per million person-years AND there is no evidence from the sitagliptin clinical trials or from other DPP4 inhibitors that this is a class effect. In addition, one must take the published report on the effect of sitagliptin on the HIP rat (a substantial part of OSE's argument in favor of placing pancreatitis under the Warnings and Precautions) with a fair degree of skepticism. Dr. Todd Bourcier, in his review of the Butler paper, points out the following:

- The amylin amino acid sequence that is amyloidogenic in the HIP rat is identical in humans, dogs and monkeys, but not in normal SD rats or in mice. Dogs and monkeys were extensively

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studied in the sitagliptin chronic toxicology studies, and no evidence of enzyme elevation or histopathologic pancreatitis was observed in these two species, despite many multiples of human exposures in these studies.

- The combination of the hIAPP transgene, a high fat diet, and high doses of sitagliptin and metformin represents an extreme model of diabetes. These rats express human IAPP, which is foreign to rodent pancreas, at levels sufficient to cause massive apoptosis of beta cells. The apoptotic effect is even greater in young animals which have an already proliferative pancreas. Then these animals are treated with a drug class known to induce beta cell proliferation (DPP4 inhibitors) and at very high drug exposure (at least 20-fold higher vs. clinical dose based on AUC). It is not possible to determine if human IAPP, hyperglycemia, or both are necessary to enable sitagliptin toxicity in the pancreas based on Butler's study. If both are required, then the adverse pancreatic effect is limited to this model, and the relevance of this model to human diabetes is already questionable.

The manuscript also conveys the idea that the concomitant use of metformin can, to a certain extent, reverse the proliferative role of sitagliptin on pancreatic ductal cells. The evidence from the cases reported with sitagliptin or sitagliptin / metformin FDC is that a substantial proportion (perhaps close to 50 %) where cases where sitagliptin was coadministered with metformin or the patient was being treated with the FDC.

Therefore, without a plausible mechanism for pancreatitis with sitagliptin and reporting rates that are lower than the background rate for the general population, and almost certainly even lower than the rate in the non-exposed diabetic population, there is no need to place "pancreatitis" under Warnings and Precautions, although it is prudent to inform HCP of this potential emerging risk by adding the term as an AR (including the listing of hemorrhagic and necrotizing pancreatitis).

Dr. Syed Ahmad, the epidemiologist who helped in the OSE review, concludes:

"It is interesting to note that sitagliptin which was approved almost six months later than exenatide, has about 2.4 million more cumulative prescriptions than exenatide, but has a smaller number of case reports of both acute pancreatitis and hemorrhagic / necrotizing pancreatitis. In conclusion, the data at hand suggests that there is a significant and clinically meaningful difference in the risk of acute pancreatitis and HNP in association with sitagliptin and exenatide and the label should convey that difference."

### OSE's recommendations:

- The risk of acute and necrotizing pancreatitis be communicated to HCP and patients through the FDA website, MedWatch Alert and / or a Dear HCP letter
- The sponsor consider a post-marketing study in human subjects to measure the effects of sitagliptin on physiological functions of pancreas, such as pancreatic enzyme secretion and activities, pancreatic fluid flow, and gallbladder contractility (a similar study was recommended to Amylin, and that sponsor is conducting the recommended study with exenatide).
- Modify the current labeling for sitagliptin and sitagliptin / metformin FDC to include acute pancreatitis and necrotizing / hemorrhagic pancreatitis with the suggested wording as follows: "Cases of acute pancreatitis and necrotizing pancreatitis have been reported in patients receiving sitagliptin (Januvia and Janumet). Patients should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. Should pancreatitis be suspected, the drug should be discontinued, supportive

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medical therapy instituted, and the patient monitored closely with appropriate laboratory studies (e.g., serum and urine amylase, amylase/creatinine clearance ratio, electrolytes, serum calcium, glucose, lipase, etc.). A search for other causes of pancreatitis as well as those conditions which mimic pancreatitis should be conducted. Alternative treatment for the underlying medical condition should be initiated as clinically indicated.”

Dr. Wang, her team leader and Division Director recommend that this labeling change be placed under Warnings and Precautions, where it will gain more attention and visibility. Dr. Ahmad recommends that this wording be placed under AR – Postmarketing Experience section of the label for these two drugs, consistent with his view that the risk of pancreatitis associated with sitagliptin is much lower than that with exenatide, where he favored the wording under Warnings and Precautions.

Dr. Ahmad’s team leader and Director sided with DPV1. Dr. Ahmad’s team leader, Dr. Allen Brinker, wrote a separate review memo, focusing on the reporting rates of pancreatitis for sitagliptin as compared to exenatide (drug-to-drug comparison); in his review, he states that the absolute count of cases of pancreatitis in the first 18 months of marketing of these products is similar, regardless of drug exposure, and regardless of the fact that the number of reports of sitagliptin-associated pancreatitis increased after the first health alert for exenatide.

Drs. Avigan and Iyasu, Division Directors of DPV1 and DEPI, respectively, co-wrote a separate memorandum, in which they focused on the comparison of cases of pancreatitis associated with sitagliptin against the national background rate (observed-to-expected analysis). In their analysis, they conclude that underreporting to AERS may be significant, and that the background may not be reliable, thus affecting both the numerator and the denominator in the reporting rate for sitagliptin and making a comparison to exenatide unreliable as well.

*Reviewer comment: the same reasons for uncertainty (imprecise estimate of underreporting, imprecise estimate of the expected risk in a specific subpopulation) are present in FDA’s analysis of postmarketing risk for other pairs of drug / adverse reaction, and the regulatory action in other circumstances has not been consistently applied.*

They also mentioned the Butler paper to inform both Dr. Wang’s decision as well as their own decision:

“Third, there appears to be growing evidence that sitagliptin may exert effects on the exocrine pancreas in conjunction with its known insulinotropic effects. High rates of pancreatic duct cell turnover and ductal metaplasia have been observed in sitagliptin-treated rats, suggesting yet undefined pleiotropic effects by this agent and possibly other members of the drug class on pancreatic exocrine physiology.”

*Reviewer comment: The growing evidence referenced comes from a single publication, which is based on a study of one model of T2DM, whereas no other supporting evidence from this mechanism has been found in chronic toxicity studies, and no reports of pancreatitis in animal models were found in the pre-clinical development of sitagliptin or other DPP4 inhibitors.*

Finally, Drs. Avigan and Iyasu speculate on the potential mechanism for development of pancreatitis in humans, as stated below:

“The AERS cases suggest the possibility that sitagliptin exposure may increase the risk of this

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condition, either through a direct effect on the pancreas or pancreatic duct outflow system, or indirectly by affecting another risk factor (e.g., effects on gallbladder motility, serum triglyceride levels, etc.)”.

*Reviewer comment: The case descriptions in AERS have not been able to provide any evidence for a mechanism by which patients with diabetes may have an increased risk of pancreatitis when treated with sitagliptin. There are no studies to date that demonstrate effect of sitagliptin (or even GLP-1) on pancreatic duct outflow, gallbladder motility or serum triglyceride levels.*

Drs. Avigan and Iyasu favor placing pancreatitis under Warnings and Precautions so that the risk gains an appropriate level of attention and because they believe that prompt discontinuation of sitagliptin will reduce or prevent the risk of progression of pancreatitis to a more severe form (hemorrhagic or necrotizing).

*Reviewer comment: From the review of AERS cases and the initial presentation, it did not appear that the cases of hemorrhagic or necrotizing pancreatitis had been initially diagnosed with acute edematous pancreatitis and after continuous treatment with sitagliptin progressed to the complicated forms. Instead, a few of the cases of pancreatitis resolved while the patients continued treatment with sitagliptin, and at least one case of rechallenge was negative. There are very few cases to inform a conclusion and regulatory action, but the literature on pancreatitis suggests that the initial presentation of a patient, in 10 to 20 % of cases, may be a complicated form (this proportion may be even higher, as the diagnoses of complicated forms are dependent on imaging characteristics, and imaging is not always available or ordered upon the diagnosis).*

Although disagreeing with the section of labeling for placement of the adverse reaction, I agree with the following language suggested by OSE for labeling:

“Cases of acute pancreatitis, including necrotizing pancreatitis, have been reported in patients receiving sitagliptin (Januvia and Janumet). Patients should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. Should pancreatitis be suspected, the drug should be discontinued, supportive medical therapy instituted, and the patient monitored closely with appropriate laboratory studies (e.g., serum and urine amylase, amylase/creatinine clearance ratio, electrolytes, serum calcium, glucose, lipase, etc.). A search for other causes of pancreatitis as well as those conditions which mimic pancreatitis should be conducted. Alternative treatment for the underlying medical condition should be initiated as clinically indicated.”

However, there is no precedent in adding the suggested text in order to expand on a specific Adverse Reaction being listed under Section 6.2 of the label (Postmarketing Adverse Reactions), under the Physician Labeling Rule (PLR). The policy under the PLR is to elevate a reported risk to a Warning and Precaution when an explanation or instruction to HCP is necessary to mitigate a risk. The language proposed by OSE, for the most part, conveys the standard of care management for a patient presenting with a diagnostic suspicion of acute pancreatitis. Therefore, the information is not essential nor it is specific for managing drug-associated pancreatitis. Labels for other drugs which list pancreatitis as Adverse Reactions (e.g., amlodipine) do not expand on the issue to recommend the appropriate management. When faced with a patient with signs and symptoms of pancreatitis, a HCP may balance the risks and benefits of holding or stopping a drug which lists pancreatitis in its label, depending on the particular clinical circumstances for that patient.

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Therefore, the OSE recommendation is to revise labeling to add pancreatitis and necrotizing / hemorrhagic pancreatitis under Warnings and Precautions.

## **5. OVERALL ASSESSMENT**

### **5.1 Conclusions**

The postmarketing experience with sitagliptin indicates a number of cases of pancreatitis (88 in the U.S. [AERS-reviewed data] and up to 142 worldwide [Merck crude count data]) have been reported. The majority has been hospitalized: 58 of the 88 U.S. cases, and four of these were treated in intensive care. Three of the cases reported worldwide were diagnosed as necrotizing or hemorrhagic pancreatitis. This is certainly a serious risk and should be addressed thoughtfully when conveying information to HCP and to the general public. But FDA must convey the risk in its appropriate context, and this reviewer acknowledges all parties involved in this review (including Merck) have been diligent in searching for the right context, even if some of the conclusions reached differed.

I conclude the risk of pancreatitis can be appropriately conveyed to HCP through labeling by adding the term as Adverse Reactions.

The factors that were important to inform this reviewer's conclusions were:

- The lack of imbalance on the rate of pancreatitis AEs in controlled sitagliptin clinical trials, as well as in the clinical trials in support of another DPP4 inhibitor recently approved: saxagliptin;
- The lack of a signal for pancreatitis in all the animal testing conducted during the sitagliptin pre-clinical development;
- The reporting rate of pancreatitis associated with sitagliptin being lower than the background rate for the general population and possibly even lower than the background rate for diabetics; in addition, the low proportion of complicated pancreatitis compared to the background proportion;
- The lack of a known plausible mechanism to support the association between sitagliptin and pancreatitis.

All of these factors have well known limitations, as discussed earlier in this review and by other reviewers as well.

In addition, placing pancreatitis under Warnings and Precautions may exert an unintended effect of discouraging new sitagliptin prescriptions in patients who may be excellent candidates for this treatment. Physicians may be afraid to prescribe sitagliptin for a patient whose risk for pancreatitis is already elevated due to being a diabetic, being obese and having elevated triglycerides, which are usual characteristics in the target population for sitagliptin. Finally, physicians may be afraid to prescribe sitagliptin because of a higher risk to themselves from malpractice lawsuits, brought in by those patients who do develop pancreatitis.

### **5.2 Recommendation on Regulatory Action**

I recommend approval of the language proposed by the applicant, specifically, to add the term "pancreatitis" under the Adverse Reactions – Postmarketing Experience section of the sitagliptin and the sitagliptin / metformin FDC labels. In addition, the listing of hemorrhagic and necrotizing

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pancreatitis should be included.

### **5.3 Recommendation on Postmarketing Actions**

I agree with the recommendation provided by the OSE team in its review, to communicate to the sponsor to consider a post-marketing study in human subjects to measure the effects of sitagliptin on physiological functions of pancreas, such as pancreatic enzyme secretion and activities, pancreatic fluid flow, and gallbladder contractility.

I also agree with the recommendations provided by Dr. Todd Bourcier, DMEP's pharmacology / toxicology reviewer, to:

- Re-analyze sections from the chronic dog and rat studies with stains for proliferative markers as was done in Butler's study. This approach has the advantage of possibly identifying a NOAEL if ductal hyperplasia is detected at all, thus providing a better basis for risk assessment.
- Whether hyperglycemia enables sitagliptin toxicity is unknown. If true, then re-analyzing tissue sections from rats and dogs as described above would be of limited value, particularly if negative results are obtained. Obtaining pancreatic histopathology data from several rodent models of diabetes (including the HIP rat) after 3 months treatment with sitagliptin could address this issue and further discern whether the human IAPP transgene is the enabling variable.
- Despite the questionable relevance of the HIP model to human diabetes, demonstration that HIP rats recapitulate clinical observations of pancreatitis could be enormously helpful in screening numerous GLP1 products currently in development. To that end, it could be investigated whether the HIP model differentiates between exenatide, liraglutide, and DPP4 inhibitors relative to pancreatic pathology.

### **5.4 Labeling Review**

I recommend approving the changes being effected to the package insert, as proposed by the applicant, Merck. In addition, the listing of hemorrhagic and necrotizing pancreatitis should be included.

In the patient package insert, the applicant recommends adding the phrase "inflammation of the pancreas" under the section titled "What are the possible side effects of Januvia". This reviewer recommends adding the following: "Severe pain in the stomach, particularly if accompanied by nausea and vomiting, may be a sign of inflammation of the pancreas. If you have these symptoms, please let your doctor know about them immediately."

### **5.5 Comments to Applicant**

Please refer to the recommendations listed in Section 5.3 (Recommendation on Postmarketing Actions) of this review document.

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## **6. APPENDICES**

### **6.1 Line-by-Line Labeling Review**

Not applicable.

### **6.2 Other Pertinent Information**

Not applicable.

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**REFERENCES**

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2. Noel RA, Braun DK, Patterson RE, Bloomgren G. Increased risk of Increased Risk of Acute Pancreatitis and Biliary Disease Observed in Patients with Type 2 Diabetes: a Retrospective, Cohort Study. *Diabetes Care* 32(5): 834-8, 2009.
3. Schwartz's Principles of Surgery –8th Ed. (2005) – Online. Chapter 32: Pancreas.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 21995	SUPPL 13		JANUVIA 100MG (SITAGLIPTIN PHOSPHATE)
NDA 21995	SUPPL 13		JANUVIA 100MG (SITAGLIPTIN PHOSPHATE)
NDA 21995	SUPPL 13		JANUVIA 100MG (SITAGLIPTIN PHOSPHATE)

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/s/

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ILAN IRONY

08/08/2009

This is a review of reports of pancreatitis in the CBE supplement. A review of cutaneous vasculitis is filed in a separate document.

MARY H PARKS

08/08/2009

Please see Division Director's memo

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 021995/S-013**

**PHARMACOLOGY REVIEW(S)**

**SUPERVISOR'S MEMO**

Date:	17 Nov 2009
RE:	NDA 21-995 25 Sept 2009 Submission Suppl 13, #138, eCTD #92 Response to FDA information request
Sponsor:	Merck
Drug/Indication	Sitagliptin (Januvia)

**Summary:****Review:**

Merck submitted a response to a series of questions from the FDA regarding the ongoing review of adverse pancreas events associated with use of sitagliptin. My review will focus primarily on the preclinical information provided in Merck's response.

Q1: Is there a mechanistic rationale to support increased risk for pancreatitis in patients treated with sitagliptin?

Merck first discussed the pharmacological and pharmacodynamic differences between sitagliptin and exenatide. Their portrayal of the differences is largely accurate in that the two drug classes result in different patterns of exposure to GLP-1 receptor agonists (direct agonism with exenatide, indirect agonism via endogenous GLP1 with sitagliptin). The difference in degree and pattern of exposure is a reasonable explanation for some adverse findings reported with exenatide but not with sitagliptin; for example, nausea and tolerability issues in patients, and thyroid C-cell tumors in rodents. *However, it not reasonable to extend this argument and state that exenatide has a greater propensity than sitagliptin to result in adverse pancreatic events, as Merck contends, until it is demonstrated that activation of GLP1r is related to pancreatic toxicity.*

Merck next discussed the preclinical studies conducted in support of sitagliptin's approval. Their conclusions match my own, which are detailed in a prior memo on this matter, that there was no evidence of pancreatic toxicity in mice, rats, dogs, or monkeys administered high doses of sitagliptin for extended periods of time. Merck further argues that aging rodents develop a degree of insulin resistance, or 'pre-diabetes' as they called it, and therefore they would have expected to pick up adverse pancreatic pathology under hyperglycemic conditions in the 2yr carcinogenicity studies. However, the degree (if any) of hyperglycemia in the 2yr studies was not determined, and slight age-related changes in blood glucose do not sufficiently model type 2 diabetes. Indeed, it is possible that age-related insulin resistance was abrogated by initiating sitagliptin administration in young normoglycemic animals. *Given these points, I disagree that*

*the contribution of hyperglycemia to potential sitagliptin-induced pancreatic toxicity has been adequately evaluated, as implied by Merck's argument.*

Merck offered a series of criticisms of Matveyenko's and Butler's publication regarding pancreatitis and ductal metaplasia associated with sitagliptin in HIP transgenic rats. My review of Butler's paper is the subject of a prior memo submitted to NDA 21995. Merck's primary arguments are the following:

#### Historical data on HIP1 rat

Butler's paper noted that pancreatitis was not observed in 89 HIP rats previously evaluated, but the specifics of that historical information were not provided. Merck claims that of those 89, only 13 were given a HFD (high fat diet). The HIP rats used in the Butler paper were administered a HFD for a total of 6 months (3m prior to sitagliptin + 3m treatment). So if true, a matched historical experience of only 13 animals diminishes the usefulness of past experience with HIP rats. Merck also contends that the animals used in Butler's paper were older (14 months) than those in the historical record (2, 5, 10 months). However, Butler's paper clearly states that animals were 2 months old at the start of the experiment which lasted a total of 6 months, so the rats were 8 months old at the end of the study. *Because a HFD, and particularly high triglycerides, could impact the incidence of pancreatitis, I agree with Merck that the historical experience with HIP rats not given a HFD is of limited usefulness; however, Merck is wrong to cite differences in age as an additional confounding factor.*

#### Additional investigative studies

Merck cited a number of investigator-conducted studies (funded by Merck) that they claim are in conflict with Butler's results. Note that Butler's study was also funded by Merck.

- **Bonner-Weir studies**

Susan Bonner-Weir is an Associate Professor at the Joslin Diabetes Center in Boston. She provided Merck with a statement describing her opinion of the histological findings of pancreatitis and ductal metaplasia in the Butler report. She contends that the pancreatic histology in Figures 7/8 of Butler's study appears similar to the histology her lab has documented in new pancreatic lobe formation observed in mice under various conditions (pancreatectomized, spontaneous, and during embryonic development). She interprets the ductal metaplasia reported by Butler as 'focal areas of regeneration' that results in formation of normal pancreatic lobes rather than tumors or signs of pre-cancerous lesions, as suggested by Butler. *Resolution of this difference in interpretation would require further basic studies, but it is nevertheless notable that an alternative hypothesis has been voiced for the pancreatic histopathology observed in the HIP rat.*

- **Merck studies**

Merck cited 3 unidentified studies with sitagliptin in murine models of type 2 diabetes intended as PD investigations on islet function. They intend to re-examine tissue sections of pancreas archived in paraffin. One study was described as evaluating streptozotocin-treated mice fed a HFD with or without sitagliptin or glipizide for 1 to 10 weeks. Pancreatic endpoints included islet cell mass and immunostaining with cell proliferation markers. Merck states that no difference was observed in Ki67 positive nuclei among groups. Results of this study are reportedly in press in *Eu J Pharmacology*.

- Other studies

Merck listed 5 other studies being conducted by academic investigators. These studies are copy/pasted below. *In general, these studies could be relevant provided that the endpoints include a thorough histological assessment of the pancreas that includes immunostaining with cell proliferation markers, and that the evaluation includes exocrine, endocrine, and ductal areas of the pancreas.*



(b) (4)

### Post-marketing Requirements

Merck has been notified that additional preclinical studies in animal models of diabetes will be part of the post-marketing requirements that address the issue of pancreatic toxicology with sitagliptin. Important elements of these studies are the following:

1. Use of diabetic models, marked by high blood glucose/triglycerides
2. At least three months duration of dosing with sitagliptin
3. Histological evaluation of exocrine and endocrine pancreas, including ducts
4. Assessment of cell proliferation markers (e.g., BrdU, Ki67, PCNA) in pancreas

Studies currently underway or already completed that include these elements would be accepted in place of new studies.

### Summary & Conclusions

Merck provided some information and arguments that counter the relevance and implications of Dr. Butler's findings in HIP rats. Some of this information is based on a different interpretation of the pancreatic histopathology (i.e., Dr. Bonner's letter), but none of the arguments are sufficient to address the gap in experimental data with sitagliptin in diabetic animal models. Therefore, the Division's post-marketing requirement for additional non-clinical data, as discussed above, remains justified.

Merck has been informed of these post-marketing requirements, so no additional communication is needed until Merck submits protocols for Division approval.

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

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/s/

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TODD M BOURCIER

11/17/2009

Review of Merck's response to Info Request; nonclin info on pancreatitis

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 021995/S-013**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: December 18, 2009

To: Mary Parks, MD, Director  
**Division of Metabolic and Endocrine Products (DMEP)**

Through: Claudia Karwoski, PharmD, Director  
**Division of Risk Management (DRISK)**  
LaShawn Griffiths, RN, MSHS-PH, BSN,  
Patient Labeling Reviewer, Acting Team Leader  
**Division of Risk Management (DRISK)**

From: Robin Duer, RN, MBA, BSN  
Patient Product Information Reviewer  
Jessica M. Diaz, RN, BSN  
Patient Product Information Reviewer  
**Division of Risk Management**

Subject: DRISK Review of Patient Labeling (Medication Guides) and  
Proposed Risk Evaluation and Mitigation Strategy (REMS)

Drug Name(s): JANUMET(sitagliptin/metformin HCl) Tablets  
JANUVIA (sitagliptin phosphate) Tablets

Application Type/Number: NDA 22-044  
NDA 21-995

Applicant/sponsor: Merck & Co., Inc.

OSE RCM #: 2009-2240

## **1 INTRODUCTION**

This review is written in response to a request by the Division of Metabolic and Endocrine Products (DMEP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) and Risk Evaluation and Mitigation Strategy (REMS) for JANUMET (sitagliptin/metformin HCl) and JANUVIA (sitagliptin phosphate). Please let us know if DMEP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

JANUMET (sitagliptin/metformin HCl) was approved on March 30, 2007; JANUVIA (sitagliptin phosphate) was approved on October 16, 2006. In a letter dated October 16, 2009, DMEP requests Merck & Company, Inc. change their patient package insert (PPI) to a Medication Guide (MG) in addition to labeling changes due to new safety information regarding increase cases of pancreatitis, specifically two cases of necrotizing pancreatitis for JANUMET (sitagliptin/metformin HCl) and JANUVIA (sitagliptin phosphate). As part of their request the MG was to be included in a proposed REMS that also includes the Timetable for Submission of Assessments.

Please send these comments to the Applicant and request a response within two weeks of receipt of DRISK's review of the REMS. Let us know if you would like to have a meeting to discuss these comments before sending to the Applicant. The DRISK review of the methodology and survey instruments, once submitted by the Applicant to evaluate the REMS, will be provided under a separate cover.

## **2 MATERIAL REVIEWED**

- Draft JANUMET (sitagliptin/metformin HCl) Prescribing Information (PI) submitted December 3, 2009 and revised by the Review Division through the current review cycle.
- Draft JANUMET (sitagliptin/metformin HCl) Medication Guide (MG) submitted November 13, 2009.
- JANUMET (sitagliptin/metformin HCl) Risk Evaluation and Mitigation Strategy (REMS), Changes Being Effectuated (CBE) Complete Response Letter dated October 16, 2009.
- JANUMET (sitagliptin/metformin HCl) proposed REMS submitted on November 13, 2009.
- Draft JANUVIA (sitagliptin phosphate) Prescribing Information (PI) submitted December 3, 2009 and revised by the Review Division through the current review cycle.
- Draft JANUVIA (sitagliptin phosphate) Medication Guide (MG) submitted November 13, 2009.
- JANUVIA (sitagliptin phosphate) Risk Evaluation and Mitigation Strategy (REMS), Changes Being Effectuated (CBE) Complete Response Letter dated October 16, 2009.
- JANUVIA (sitagliptin phosphate) proposed REMS submitted November 13, 2009.

### **3 RESULTS OF REVIEW**

**In our review of the Medication Guides, we have:**

- simplified wording and clarified concepts where possible
- ensured that the MGs are consistent with the PIs
- removed unnecessary or redundant information
- ensured that the MGs meet the Regulations as specified in 21 CFR 208.20
- ensured that the MGs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

**In our review of the proposed REMS**, we have ensured it meets the statutory requirements under the Food and Drug Administration Amendments Act (FDAAA) of 2007.

### **4 CONCLUSIONS AND RECOMMENDATIONS**

DRISK concurs with the MG and the elements of the REMS with revisions provided in this review.

Please note, the REMS timetable for submission of the assessments is required to be approved as part of the REMS, but not the Applicant's proposed information about the details of the REMS evaluation (methodology/instruments). The methodology and instruments **do not** need to be reviewed or approved prior to approval of the REMS.

We have the following comments and recommendations for the DNP and Applicant with regard to the MG and the proposed REMS modification.

#### **Comments to DMEP:**

Our annotated MGs are appended to this memo.

Appendices:

A-JANUMET Marked Copy

B-JANUMET Clean Copy

C-JANUVIA Marked Copy

D-JANUVIA Clean Copy

Any additional revisions to the PI should be reflected in the MG.

#### **Comments to Merck & Company, Inc:**

See the appended JANUMET (sitagliptin/metformin HCl) and JANUVIA (sitagliptin phosphate) REMS proposal (Appendices E and F of this memo) for track changes corresponding to comments in this review.

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.

Please let us know if you have any questions.

38 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21995	SUPPL-13	MERCK CO INC	JANUVIA 100MG (SITAGLIPTIN PHOSPHATE)
NDA-22044	SUPPL-11	MERCK AND CO INC	JANUMET(PHOSPHATE/METFORMIN HCL FIXED DO

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/s/

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JESSICA M DIAZ  
12/18/2009

CLAUDIA B KARWOSKI  
12/18/2009  
concur

## Risk Evaluation and Mitigation Strategy (REMS) Memorandum

**U.S. FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF DRUG EVALUATION II  
DIVISION OF METABOLISM AND ENDOCRINOLOGY PRODUCTS**

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**NDA #:** 21-995  
**Products:** Januvia® (sitagliptin) tablets, 25 mg, 50 mg, and 100 mg  
**SPONSOR:** Merck & Co., Inc.  
**FROM:** Mary H. Parks, M.D.  
**DATE:** October 14, 2009

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Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a REMS for an approved drug 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)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug
- (F) Whether the drug is a new molecular entity (NME).

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 section 505-1(b)(3) of the FDCA.

After consultation between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary to ensure that the benefits of Januvia (sitagliptin) outweigh its risks. In reaching this determination, we considered the following:

- A. Approximately 24 million people in the U.S. have diabetes of whom more than one-third will require more than one anti-diabetic agent to maintain adequate glycemic control within several years of initiation of drug therapy. From marketing (October 2006) through December 2008, an estimated 8.6 million prescriptions of Januvia (sitagliptin) have been dispensed.
- B. Patients with type 2 diabetes who require anti-diabetic medication for glycemic control are at risk for a variety of complications including heart disease, stroke, blindness, kidney failure, nervous system damage, amputations, and death if untreated. Januvia (sitagliptin) is an

option for those individuals who are inadequately treated with lifestyle modification or other anti-diabetic therapies.

- C. Januvia (sitagliptin) has been shown to achieve a mean placebo-adjusted reduction in HbA<sub>1c</sub> of 0.8% when given as monotherapy and a mean placebo-adjusted reduction in HbA<sub>1c</sub> of 2.1% when used in combination with metformin. A reduction in HbA<sub>1c</sub> is associated with reduced rates of microvascular complications of diabetes (retinopathy, nephropathy and neuropathy) and possibly, with reduced rates of adverse macrovascular outcomes.
- D. The expected duration of therapy is over a patient's lifetime.
- E. In addition to post-marketing reports of acute pancreatitis, including necrotizing pancreatitis, Januvia (sitagliptin) has been associated with various other adverse effects that involve the gastrointestinal tract, including nausea and diarrhea, hypoglycemia when used in combination with a sulfonylurea, and hypersensitivity reactions.
- F. This product is a new molecular entity (NME).

In accordance with section 505-1 of the FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Januvia (sitagliptin). FDA has determined that Januvia (sitagliptin) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Januvia (sitagliptin). FDA has determined that Januvia (sitagliptin) is a product for which patient labeling could help prevent serious adverse effects and that has a serious risk (relative to benefits) of which patients should be made aware because information concerning the risk could affect patients' decisions to use, or continue to use Januvia (sitagliptin).

The elements of the REMS will be a Medication Guide and a timetable for submission of assessment of the REMS. To protect the public health, FDA is requiring submission of the proposed REMS within 30 days after notifying Merck that a REMS is required.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
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 13	MERCK CO INC	JANUVIA 100MG (SITAGLIPTIN PHOSPHATE)

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/s/

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AMY G EGAN  
10/16/2009

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 021995/S-013**

**OTHER REVIEW(S)**

**Division of Metabolism and Endocrinology Products**  
**REGULATORY PROJECT MANAGER REVIEW**

**Application Number:** NDA 21-995/S-013

**Name of Drug:** Januvia (sitagliptin) Tablets

**Applicant:** Merck and Co, Inc.

**Material Reviewed:**

Submission Date  
December 03, 2009

Receipt Date  
December 03, 2009

Document Type  
Package Insert (PI)

**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 PPAR $\gamma$  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 October 10, 2008, and approved on October 20, 2008, for Supplement-009.

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, therefore, is in reference to the Package Insert only.

## Review

### Package Insert:

The PI, submitted on December 03, 2009, was compared to the currently approved PI for Januvia, approved on October 20, 2008. The following changes were found:

### OVERALL

- The identifying number at top of each page was changed from “9762706” to “97627XX”.

*Note: This change is acceptable.*

- Since a new sub-section entitled “**5.1 Pancreatitis**” has been added at the beginning of the Warnings and Precautions section of the Full Prescribing Information, the previous four sub-sections were re-numbered “5.2” through “5.5”. References made to these sub-sections throughout the Package Insert were therefore changed accordingly.

*Note: This change is acceptable.*

### HIGHLIGHTS OF PRESCRIBING INFORMATION

- Recent Major Changes was changed from:

**Warnings and Precautions**  
**Macrovascular Outcomes (5.4) 07/2008**

to:

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

*Note: This change is acceptable.*

- Under Indications and Usage, Important Limitations of Use, the following was added as a third bullet point:

**JANUVIA has not been studied in patients with a history of pancreatitis. (1.2, 5.1)**

*Note: This addition is acceptable. This text was requested in the supplement request letter dated October 16, 2009.*

- Under Warnings and Precautions, the following was added as the first bullet point:

**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)**

*Note: This addition is acceptable. This text was requested in the supplement request letter dated October 16, 2009.*

- 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.**

*Note: The reference to the FDA-approved patient labeling or Medication guide will need to be removed, since the Medication Guide has not yet been approved for circulation. When the Medication Guide is approved, this text can be re-inserted in the PI.*

- The “Revised” Date was changed from “10/2008” to (b) (4).

*Note: This change is acceptable.*

## FULL PRESCRIBING INFORMATION: CONTENTS

- Under Warnings and Precautions, “**Pancreatitis**” was added as sub-section 5.1. The remaining four sub-sections were re-numbered accordingly.

*Note: This addition is acceptable.*

## FULL PRESCRIBING INFORMATION

- Under Indications and Usage, Important Limitations of Use (1.2), the following was added as a third bullet point:

**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).]**

*Note: This addition is acceptable. This text was requested in the supplement request letter dated October 16, 2009.*

- Under Warnings and Precautions (5), the following was added as the first sub-section 5.1:

### **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.**

*Note: This addition is acceptable. This text was requested in the supplement request letter dated October 16, 2009.*

- Under Warnings and Precautions (5), the remaining four sub-sections were re-numbered “5.2” through “5.5”.

*Note: This change is acceptable.*

- Under Adverse Reactions, Postmarketing Experience (6.2), the following was added to the second paragraph, shown here underlined:

**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)].**

*Note: This addition is acceptable.*

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

**See FDA-Approved Patient Labeling.**

to:

**See FDA-Approved Medication Guide.**

*Note: The reference to the FDA-approved patient labeling or Medication guide will need to be removed, since the Medication Guide has not yet been approved for circulation. When the Medication Guide is approved, this text can be re-inserted in the PI.*

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

**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)].**

*Note: This addition is acceptable.*

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

**Physicians should instruct their patients to read the Patient Package Insert before starting JANUVIA therapy and to reread each time the prescription is renewed.**

to:

**Physicians should instruct their patients to read the Medication Guide before starting JANUVIA therapy and to reread each time the prescription is renewed.**

*Note: The reference to the FDA-approved patient labeling or Medication guide will need to be removed, since the Medication Guide has not yet been approved for circulation. When the Medication Guide is approved, this text can be re-inserted in the PI.*

END OF PACKAGE INSERT

- The identifying number was changed from “9762706” to “97627XX”.

*Note: This change is acceptable.*

- The following copyright date was added, shown here underlined:

**COPYRIGHT © 2006, 2007, 2009 MERCK & CO., Inc.**

*Note: This change is acceptable.*

**Conclusion**

An approval letter for NDA 21-995/S-013 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/12.08.09  
Clearance: L.Aljuburi/12.08.09  
Finalized: M.Hai/12.28.09

CSO LABELING REVIEW

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

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/s/

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MEHREEN HAI  
12/28/2009



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: October 9, 2009

To: Mary Parks, MD, Director  
**Division of Metabolic and Endocrinology Products**

Through: Claudia Karwoski, Pharm.D., Director  
**Division of Risk Management (DRISK)**

Sharon R. Mills, BSN, RN, CCRP  
Senior Patient Labeling Reviewer, Acting Team Leader  
**Division of Risk Management**

From: Robin Duer, MBA, BSN, RN  
Patient Labeling Reviewer  
**Division of Risk Management**

Melissa Hulett, MSBA, BSN, RN  
Patient Labeling Reviewer  
**Division of Risk Management**

Subject: DRISK Review of Patient Labeling (Patient Package Insert)

Drug Name(s): Januvia (sitagliptin) Tablets

Application Type/Number: NDA 21-995

Submission Number: S-010, S-011, S-013

Applicant/sponsor: Merck Pharmaceuticals Research

OSE RCM #: 2009-461

## **1. INTRODUCTION**

This review is written in response to a request by the Division of Metabolic and Endocrinology Products (DMEP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for Januvia (sitagliptin) Tablets. Please let us know if DMEP would like a meeting to discuss this review or any of or changes prior to sending to the Applicant.

## **2. MATERIAL REVIEWED**

- Draft Januvia (sitagliptin) Tablets Prescribing Information (PI) submitted December 18, 2008 (S-010), December 19, 2008 (S-011), and March 5, 2009 (S-013) and revised by the Review Division throughout the current review cycle.
- Draft Januvia (sitagliptin) Tablets Patient Package Insert (PPI) submitted on December 18, 2008 (S-010), December 19, 2008 (S-011), and March 5, 2009 (S-013) and revised by the Review Division throughout the current review cycle.

## **3. RESULTS OF REVIEW**

In our review of the PPI, we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated PPI is appended to this memo. Any additional revisions to the PI should be reflected in the PPI.

Please let us know if you have any questions.

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/s/  
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MELISSA I HULETT  
10/09/2009

CLAUDIA B KARWOSKI  
10/09/2009  
concur

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 021995/S-013**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>Mail: OSE</b>		FROM: Julie Marchick, Regulatory Project Manager, Division of Metabolism and Endocrinology Products, (301) 796-1280		
DATE March 12, 2009	IND NO. N/A	NDA NO. 21-995 and 22-044	TYPE OF DOCUMENT CBE Labeling Supplement	DATE OF DOCUMENT March 5, 2009
NAME OF DRUG Januvia (sitagliptin) Tablets Janumet (sitagliptin/metformin HCl FDC) Tablets		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Anti-diabetic	DESIRED COMPLETION DATE <b>August 5, 2009</b>
NAME OF FIRM: Merck				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b>				
<p>Merck submitted CBE labeling supplements NDA 21-995/S-013 for Januvia (sitagliptin) and NDA 22-044/S-011 for Janumet (sitagliptin/metformin HCl FDC), which provide for addition of cutaneous vasculitis under the Postmarketing Experience subsection of the Adverse Events section of the Package Insert.</p> <p>We request an AERS search for cases of all types of vasculitis, including cases reported as cutaneous vasculitis, associated with the use of sitagliptin. Please comment on whether you agree with Merck that cutaneous vasculitis should be placed in the postmarketing section of the label.</p> <p>The labeling supplements can be found in the edr:          NDA 21-995/S-013, dated March 5, 2009: <a href="#">\CDSESUB1\EVSPROD\NDA021995\0072</a>          NDA 22-044/S-011, dated March 5, 2009: <a href="#">\CDSESUB1\EVSPROD\NDA022044\0048</a></p> <p>The user fee goal dates for both supplements are September 5, 2009. We request that the review be complete by August 5, 2009.</p>				
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

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Julie Marchick  
3/12/2009 09:17:43 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>Mail: OSE/DRISK</b>		FROM: Julie Marchick, Regulatory Project Manager, Division of Metabolism and Endocrinology Products, (301) 796-1280		
DATE March 11, 2009	IND NO. N/A	NDA NO. 21-995 and 22-044	TYPE OF DOCUMENT CBE Labeling Supplement	DATE OF DOCUMENT March 5, 2009
NAME OF DRUG Januvia (sitagliptin) Tablets Janumet (sitagliptin/metformin HCl) Tablets		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Anti-Diabetic	DESIRED COMPLETION DATE <b>August 21, 2009</b>
NAME OF FIRM: Merck				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b>  Merck submitted CBE labeling supplements NDA 21-995/S-013 for Januvia (sitagliptin) and NDA 22-044/S-011 for Janumet (sitagliptin/metformin HCl FDC), which provide for addition of pancreatitis and cutaneous vasculitis under the Postmarketing Experience subsection of the Adverse Events section of the Package Inserts. The sponsor also proposed addition of "inflammation of the pancreas" to the Patient Package Inserts (PPIs). Please review the revised PPIs submitted by Merck.  The labeling supplements can be found in the eDr: NDA 21-995/S-013, dated March 5, 2009: <a href="#">\ICDSESUB1\EVSPROD\NDA021995\0072</a> NDA 22-044/S-011, dated March 5, 2009: <a href="#">\ICDSESUB1\EVSPROD\NDA022044\0048</a>  The user fee goal dates for both supplements are September 5, 2009. We request that the review be complete by August 21, 2009.				
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SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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Julie Marchick  
3/11/2009 10:11:38 AM



NDA 21-995/S-013

**CBE-0 SUPPLEMENT**

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 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-013

Date of Supplement: March 5, 2009

Date of Receipt: March 5, 2009

This supplemental application, submitted as "Supplement - Changes Being Effected" 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.

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 May 4, 2009, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be **September 5, 2009**.

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

NDA 21-995/S-013

Page 2

If you have questions, please call me at (301) 796-1280.

Sincerely,

*{See appended electronic signature page}*

Julie Marchick, MPH  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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Julie Marchick  
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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>Mail: OSE</b>		FROM: Julie Marchick, Regulatory Project Manager, Division of Metabolism and Endocrinology Products, (301) 796-1280		
DATE March 11, 2009	IND NO. N/A	NDA NO. 21-995 and 22-044	TYPE OF DOCUMENT CBE Labeling Supplement	DATE OF DOCUMENT March 5, 2009
NAME OF DRUG Januvia (sitagliptin) Tablets Janumet (sitagliptin/metformin FDC) Tablets		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Anti-diabetic	DESIRED COMPLETION DATE <b>August 5, 2009</b>
NAME OF FIRM: Merck				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input checked="" type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>II. BIOMETRICS</b>				
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<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
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<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b>  Merck submitted CBE labeling supplements NDA 21-995/S-013 for Januvia (sitagliptin) and NDA 22-044/S-011 for Janumet (sitagliptin/metformin HCl FDC), which provide for addition of pancreatitis under the Postmarketing Experience subsection of the Adverse Events section of the Package Insert.  We request an AERS search for cases of acute pancreatitis (including the hemorrhagic and necrotizing forms) associated with the use of sitagliptin. Because Merck states in their submission that there were numerous reports of pancreatitis in AERS for other commonly used oral anti-diabetic agents, we request that you use other anti-diabetic agents (including metformin, pioglitazone, rosiglitazone, glimepiride, and glipizide) as comparators in your AERS analysis and provide both crude counts as well as proportional reporting rates. Please also provide the background rate for acute pancreatitis in the diabetic population as a reference. Do you agree with Merck that pancreatitis should be placed in the postmarketing section of the label?  The labeling supplements can be found in the eDr: NDA 21-995/S-013, dated March 5, 2009: <a href="#">\CDSESUB1\EVSPROD\NDA021995\0072</a> NDA 22-044/S-011, dated March 5, 2009: <a href="#">\CDSESUB1\EVSPROD\NDA022044\0048</a>  The user fee goal dates for both supplements are September 5, 2009. We request that the review be complete by August 5, 2009.				

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Julie Marchick  
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