



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, 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.**

(b) (4)

(b) (4)

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

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/s/

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