DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022044/S-011 **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-011) dated and received March 5, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Janumet (sitagliptin/metformin HCl) 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-011.

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 Janumet (sitagliptin/metformin HCl) tablets. This information pertains to the risk of acute pancreatitis, including necrotizing pancreatitis, with the use of Janumet (sitagliptin/metformin HCl).

In response to the safety labeling change requirement outlined in our October 16, 2009, action letter, S-011 (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 ~~strikethrough~~):

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

JANUMET has not been studied in patients with a history of pancreatitis. (b) (4)

(1. (b) (4) 5.2).

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 JANUMET.** (b) (4)

(5.2 (b) (4)).

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

(b) (4) **JANUMET 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 JANUMET.** ***[See Warnings and Precautions (5.2).]*** (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 JANUMET. After initiation of JANUMET,** (b) (4) **patients should be observed carefully for signs and symptoms of pancreatitis** (b) (4) **If pancreatitis is suspected, JANUMET 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 JANUMET.** (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 (5.14)]*; upper respiratory tract infection; hepatic enzyme elevations; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis *[see Limitations of Use (1); Warnings and Precautions (5.2)]*.

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

Patients should be informed that acute pancreatitis has been reported during postmarketing use of JANUMET. 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 JANUMET and contact their physician if persistent severe abdominal pain occurs *[see Warnings and Precautions (5.2)]*.

The Package Insert is approved under S-011, 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 (b) (4)". 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)

(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 the use of Janumet (sitagliptin/metformin HCl), 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 Janumet (sitagliptin/metformin HCl). (b) (4)

(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

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