DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

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

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

Dear Dr. Swanson:

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

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

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

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

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

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

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

CARTON AND IMMEDIATE CONTAINER LABELS

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

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

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

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

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

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

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

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

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

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

NDA 021995 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 021995
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

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

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

POSTMARKETING REQUIREMENTS UNDER 505(o)

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

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

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

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

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

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

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

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

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

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

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

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

PROMOTIONAL MATERIALS

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

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

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

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

LETTERS TO HEALTH CARE PROFESSIONALS

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

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

REPORTING REQUIREMENTS

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

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