CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 021995/S-014

Trade Name: **JANUVIA**

Generic Name: **Sitagliptin**

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

Approval Date: 02/26/2010

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

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NDA 021995/S-014

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APPLICATION NUMBER:

NDA 021995/S-014

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

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

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

Dear Dr. Swanson:

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

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

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

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

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

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

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

CARTON AND IMMEDIATE CONTAINER LABELS

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

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

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

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

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

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

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

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