CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202270Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202270

COMPLETE RESPONSE

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

Dear Dr. Swanson:

Please refer to your New Drug Application (NDA) dated September 23, 2010, received September 23, 2010, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for JANUMET XR (sitagliptin and extended-release metformin hydrochloride fixed-dose combination) Tablets, 100mg/1000mg, 50mg/500mg, and 50mg/1000mg.

We acknowledge receipt of your amendments dated September 30, November 11 and 12, December 16 and 23, 2010; and January 10(2), January 21, March 25, April 11, 13, 27, and 29, May 6 (2), 18, 27, and 31, June 3, 22, and 30, and July 1 (2), 11, 12 (2), and 18, 2011.

We also acknowledge receipt of your amendment dated July 21, 2011, which was not reviewed for this action. This amendment contained updated datasets in SAS transport files for the complete study report (CSR) for Study 147-00, entitled "A Definitive Bioequivalence Study for Sitagliptin/Metformin XR FDC Tablets in Healthy Subjects".

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL PHARMACOLOGY

Please submit the updated CSR for Study 147-00. You may incorporate applicable sections of the amendment dated July 21, 2011 by specific reference as part of your response to the deficiencies cited in this letter.

FACILITY INSPECTIONS

During the pre-approval inspection of the Arecibo, Puerto Rico manufacturing facility on March 28 through April 14, 2011, our field investigators conveyed deficiencies, which were documented on the Form FDA 483 on April 14, 2011, to the representatives of the facility.

Satisfactory resolution of these deficiencies is required before this application may be approved. Specifically:

1. Your response to Observation 1A [redacted (b) (4)]

2. Additionally, the inspection revealed that the facility was not ready to meet the application commitment of using [redacted (b) (4) (b) (4)] Specifically, you could not provide data or procedures to support the use of [redacted (b) (4)] to the Arecibo facility was not complete at the time of the inspection.

SAFETY UPDATE

When you respond to the above deficiency, 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.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

In our letter dated December 3, 2010, we notified you that a risk evaluation and mitigation strategy (REMS) was required for JANUMET XR (sitagliptin and extended-release metformin hydrochloride fixed-dose combination) to ensure the benefits of the drug outweighed the risks of acute pancreatitis, including necrotizing pancreatitis. We indicated that your REMS must include a Medication Guide and a timetable for submission of assessments of the REMS.

We also refer to our April 14, 2011 Supplemental New Drug Application (sNDA) approval letters for JANUVIA (sitagliptin), sNDA 021995/S-017 and JANUMET (sitagliptin and metformin hydrochloride), sNDA 022044/S-016 that informed you that we were releasing the requirement for the approved REMS for those products.

We acknowledge receipt of your submission dated December 16, 2010 that included a REMS proposal for JANUMET XR (sitagliptin and extended-release metformin hydrochloride fixed-dose combination). We have determined that maintaining a Medication Guide as part of the approved labeling will be adequate to address the serious and significant public health concern and will meet the standard in 21 CFR 208.1. Therefore, a REMS will not be necessary to ensure that the benefits of JANUMET XR (sitagliptin and extended-release metformin hydrochloride fixed-dose combination) outweigh the risks described above. We will notify you if we become aware of new safety information and make a determination that a REMS is necessary.

We remind you that the Medication Guide will continue to be part of the approved labeling in accordance with 21 CFR 208.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. 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.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Raymond Chiang, M.S., Regulatory Project Manager, at (301) 796-1940.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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