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APPLICATION NUMBER:
200153Orig1s000

OTHER ACTION LETTERS



NDA 200153

COMPLETE RESPONSE

Merck Sharp & Dohme Corp.
Attention: Catherine Kohler, PharmD
Director, Worldwide Regulatory Affairs
P.O. Box 1000, UG2D-027
North Wales, PA 19454

Dear Dr. Kohler:

Please refer to your New Drug Application (NDA) dated April 28, 2011, received April 29, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Atozet (ezetimibe/atorvastatin) Tablets, 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg.

We acknowledge receipt of your amendments dated April 29, June 23, July 7 and 22, August 10, 22 and 26, September 12, 14 and 22 (2), October 11, 17, and 31, and November 11 and 14, 2011.

The April 28, 2011, submission constituted a complete response to our October 29, 2009, action letter.

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

This application was submitted to support approval of four fixed-dose combination tablet formulations containing 10 mg ezetimibe and either 10, 20, 40, or 80 mg atorvastatin calcium for the treatment of patients with primary hypercholesterolemia, mixed hyperlipidemia, and homozygous familial hypercholesterolemia. All submitted safety and efficacy trials were conducted with coadministration of separate ezetimibe and atorvastatin tablets.

Study 145 (A Study to Evaluate the Definitive Bioequivalence of [Atozet] with Marketed Products) was conducted to bridge the proposed 10 mg/10 mg, 10 mg/20 mg, and 10 mg /80 mg of ezetimibe/atorvastatin calcium fixed-dose combination tablet products with coadministration of corresponding previously approved individual ezetimibe tablets and atorvastatin calcium tablets, respectively. The 90% CI of atorvastatin C_{max} GMR shows that the atorvastatin component of the proposed 10 mg/20 mg ezetimibe/atorvastatin calcium fixed-dose combination

tablet is not bioequivalent to the coadministration of the individual 10 mg ezetimibe tablet plus 20 mg atorvastatin calcium tablet.

Study 183 (A Study to Evaluate the Definitive Bioequivalence of [Atozet] with U.S. Marketed Products) was conducted to bridge the proposed 10 mg/40 mg of ezetimibe/atorvastatin calcium fixed-dose combination tablet product with coadministration of corresponding previously approved individual ezetimibe tablets and atorvastatin calcium tablets. The 90% CI of atorvastatin C_{max} GMR shows that the atorvastatin component of the proposed 10 mg/40 mg ezetimibe/atorvastatin calcium fixed-dose combination tablet is not bioequivalent to the coadministration of the individual 10 mg ezetimibe tablet plus 40 mg atorvastatin calcium tablet.

Since this application does not contain clinical efficacy and safety data for the four strengths of proposed fixed-dose combination market products, bioequivalence results are fundamental to bridge the clinical efficacy and safety data for the coadministration of relevant strengths of individual innovator products to the corresponding proposed fixed-dose combination products. Data from pharmacokinetic/pharmacodynamic modeling were not adequate to overcome the failed bioequivalence results.

We acknowledge that the 10/10 mg and 10/80 mg ezetimibe/atorvastatin calcium fixed-dose combination tablets are bioequivalent to the coadministration of the individual 10 mg ezetimibe tablet plus the individual 10 mg and 80 mg atorvastatin calcium tablets; however, given that the 10/20 mg ezetimibe/atorvastatin calcium fixed-dose combination tablet is one of the proposed starting doses and the 10/20 mg and 10/40 mg ezetimibe/atorvastatin calcium fixed-dose combination tablets will likely be the most commonly prescribed dosage strengths, we do not believe it would be in the best interest of patients to have only two of four dosage strengths available for use.

To address the aforementioned deficiencies, one option would be to reformulate the 10 mg/20 mg ezetimibe/atorvastatin calcium and 10 mg/40 mg ezetimibe/atorvastatin calcium fixed-dose combination tablets so as to demonstrate bioequivalence for both atorvastatin and ezetimibe to the coadministration of corresponding individual innovator ezetimibe tablet plus atorvastatin calcium tablet. If you believe you can adequately address the deficiencies in another manner (e.g., clinical pharmacodynamic data), we strongly encourage you to discuss your approach with the Division.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(i)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

SAFETY UPDATE

When you respond to the above deficiencies, 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.

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 Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Eric Colman, MD
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

ERIC C COLMAN
02/29/2012