CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125522Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125522/ Original 2

COMPLETE RESPONSE

Amgen, Inc.
Attention: Marc Kubasak, PhD
Senior Manager, Regulatory Affairs
One Amgen Center Drive, Mail Stop 17-2-B
Thousand Oaks, CA 01320-1799

Dear Dr. Kubasak:

Please refer to your Biologics License Application (BLA) dated and received August 27, 2014, submitted under section 351(a) of the Public Health Service Act for Repatha (evolocumab), 140 mg/mL.

We acknowledge receipt of your amendments dated September 16, 23, 24, and 29, October 10, 13, 22, 23, 27, 28, and 31, November 3, 5, 24 (2), December 11 and 16 (2), and 17, 2014, and January 8, 12, and 29, February 17, and 26 (2), March 2, 5 (2), 16 (2), 24, 25, 27, and 30, April 2, 3 (2), 8, 9, 20, 21, 23, 24 (2), and 27, May 5, 7 (2), 8, 13, 14, 18, and 22 (2), June 1, 3, 4 (2), 5(2), 8, 9, 10, 15, 17, 22, 24 (2), 26, July 8, 15, and 20, August 11, 14(2), 18, 25(5), and 26(3), 2015.

BLA 125522 provides for the use of Repatha (evolocumab) for the following indications which, for administrative purposes, we have designated as follows:

- BLA 125522/Original 1 - Repatha is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C. Repatha is also indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C. This application only includes a 420 mg once monthly dosing regimen for the HoFH indication.
- BLA 125522/Original 2 – Repatha is indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C. This application only includes a 420 mg every two weeks dosing regimen.

The subject of this action letter is BLA 125522/Original 2. A separate action letter will be issued for BLA 125522/Original 1.

All future submissions to BLA 125522/Original 1 and BLA 125522/Original 2 should specify the BLA number and the Original number to which each submission pertains.

We have completed the review of BLA 125522/Original 2, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

CLINICAL

Insufficient clinical data were provided to describe the effect of the 420 mg every two week dosage in labeling for the treatment of homozygous familial hypercholesterolemia in patients on other lipid-lowering therapies who require additional lowering of LDL-C. Specifically, the submitted data were inadequate to describe for providers what incremental benefit, if any, is achieved by doubling the dosing frequency of 420 mg once monthly to 420 mg every two weeks. Additional information from adequate and well-controlled study(ies) will be required to better characterize this dosing regimen.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 601.14(b)]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. The safety update should include data from all non-clinical and clinical studies 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 for the proposed indication using the same format as the initial submission.
    - Present tabulations of the new safety data combined with the initial data.
    - Include tables that compare frequencies of adverse events in the initial data with the retabulated frequencies described in the bullet above.

Reference ID: 4772571

- 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 study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study 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 initial data.

6. Provide updated exposure information for the clinical 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 601.3(b). 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 601.3(c). 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.

You may request a meeting or teleconference with us to discuss what steps you need to take before BLA 125522/Original 2 may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between 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 for the 420 mg dose administered every 2 weeks in patients with homozygous familial hypercholesterolemia who require additional lowering of LDL-C until you have been notified in writing that this application is approved.

If you have any questions, call Kati Johnson, Senior Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

Reference ID: 4772571

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/s/

CURTIS J ROSEBRAUGH
08/27/2015