CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103234Orig1s5166

<u>OTHER ACTION LETTERS</u>

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BLA STN 103234/5166

COMPLETE RESPONSE
April 27, 2010

Amgen, Incorporated
Attention: Annie Dang, J.D.
Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop: 17-2-B
Thousand Oaks, CA 91320

Dear Mrs. Dang:

Please refer to your supplement to your biologics license application (BLA), dated December 20, 2007, received December 26, 2007, submitted under section 351 of the Public Health Service Act for Epogen/Procit (epoetin alfa).

This supplement proposes to amend your BLA for Aranesp with the following:

1. Final reports, datasets and results of analyses for multiple studies/clinical trials as a partial response to requests for additional information from the May 10, 2007, Oncologic Drugs Advisory Committee (ODAC),
2. A revised package insert to conform to the labeling content and format requirements specified in 21 CFR 201.56(d) and 201.57, and
3. A modified Risk Evaluation and Mitigation Strategy (REMS) that includes an updated Medication Guide and updated REMS-associated documents to provide consistency with the revised package insert.

We acknowledge receipt of your amendments dated January 18, 2008, January 31, 2008, April 23, 2008, May 30, 2008, June 13, 2008, August 29, 2008, October 15, 2008, October 17, 2008, January 14, 2009, February 19, 2009, October 23, 2009, October 29, 2009, November 3, 2009, January 12, 2010, January 15, 2010, January 28, 2010, March 17, 2010, March 22, 2010, March 23, 2010, and April 12, 2010.

The amendment dated October 23, 2009, received October 26, 2009, constituted a complete response to our October 24, 2008, action letter.

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

LABELING

We have been unable to reach agreement with you on the proposed labeling. We request that you submit draft labeling that incorporates the revisions in the attached labeling. In addition, submit updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

When responding to this letter, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Epogen/Procrit (epoetin alfa) was originally approved on February 16, 2010. The REMS consists of a Medication Guide, communication plan, elements to assure safe use, implementation system, and a timetable for submission of assessments of the REMS.

We acknowledge the submission of your proposed modified REMS dated April 12, 2010, received April 13, 2010, that contains revisions to the REMS document, Medication Guide, various elements to assure safe use-related documents, and a REMS assessment. We are unable to approve your proposed modified REMS until we agree on the labeling as changes to the labeling affect the REMS. We will continue discussion of your proposed REMS modification after your complete response to this action letter has been submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or withdraw the application. If you do not take any of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). A resubmission must fully address all the deficiencies listed, and will start a new review cycle. A partial response to this letter may not be reviewed and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss the steps necessary for approval. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry on *Formal Meetings Between FDA and Sponsors or Applicants,* February, 2009 at
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf

If you have any questions, call Mona Patel, Regulatory Project Manager, at (301) 796-4236.

Sincerely,

/Patricia Keegan/
Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosures:
- Package Insert
- Patient Instructions for Use
- Medication Guide

39 Page(s) of Draft Labeling has been Withheld in Full immediately following this page as B4 (CCI/TS)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

COMPLETE RESPONSE

Our STN: BL 103234/5166

Amgen, Incorporated
Attention: Neal Storm, M.S., M.B.A.
Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop: 17-2-B
Thousand Oaks, CA 91320

OCT 2 4 2008

Dear Mr. Storm:

Please refer to the supplement to your biologics license application, dated December 20, 2007, received December 26, 2007, submitted under section 351 of the Public Health Service Act for epoetin alfa (Epogen/Procrit).

This supplement proposes to revise the package insert and patient package insert labeling based on recommendations from the May 10, 2007, Oncology Advisory Committee Meeting (ODAC) as supported by new analyses of pooled data from multiple studies and to convert the package insert to meet the requirements as specified in 21 CFR 201.56-57.

We acknowledge receipt of your amendments dated January 18, 2008, January 31, 2008, April 23, 2008, May 30, 2008, June 13, 2008, August 29, 2008, October 15, 2008, and October 17, 2008.

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

CLINICAL/STATISTICAL

1. If you intend to support labeling changes based on the results of the studies listed below, please provide study specific datasets containing all primary data captured on the case report forms associated with each study:

   CC2574-P-174
   EPO-INT-1 (P416)
   EPO-INT-2 (P467)
   EPO-INT-3
   J89-040
   CISPLATIN: I88-036, 87-018, 87-019
   NON-CISPLATIN: I88-037, 87-016, 87-017

Additionally, please provide copies of case report forms and narrative summaries for all deaths and dropouts for the following studies:

CC2574-P-174
EPO-INT-2 (P-467)
EPO-INT-3

We acknowledge your communication dated August 29, 2008, that you are unable to find case report forms for Study EPO-INT-1. We further acknowledge that for Study EPO-CAN-15 electronic case report forms were used. Please provide printed copies of the case report forms in a reviewable format for this study.

NONCLINICAL

2. Given the multiple dosing schedules listed in the labeling and the varied testing schedules employed, we are unable to determine the source of the data used to derive the multiples of human exposure from the rat and rabbit reproductive toxicology studies (contained in Section 8.2 of the label). Please identify the source of these data by study number, and whether they were submitted to the original BLA application, or to subsequent supplement application(s). Please also provide copies of the final study reports for each study from which these data were obtained.

LABELING

3. Submit the additional information as requested in the comments embedded in the attached labeling. In your response, specify the location of the information in your license application that supports your revised labeling. If such information, which also includes the datasets and analysis programs necessary to generate the information cited, was not previously submitted, you should provide the information in your response to this letter.

4. Please submit revised labeling that incorporates our proposed revisions in the attached labeling.

   To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes. In addition, submit updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

We acknowledge that your submission also included revisions to the patient package insert. However, since the time of this submission, the patient package insert has been converted to a single sheet containing the Medication Guide and Patient Instructions for Use. Therefore, we have not provided comments regarding the patient package insert. In your response to this complete response letter, please include all associated approved labeling for all Epogen/Procrit product formulations (package insert, medication guide, and patient instructions for use). In addition, please ensure that the labeling provided in your response has been updated to reflect any new labeling approved in the interim of receipt of this letter and your formal submission containing a complete response.

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.

5. Describe in detail any significant changes or findings in the safety profile.

6. 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.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

7. 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.

8. 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.

9. 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.

10. Provide updated exposure information for the clinical trials (e.g. number of subjects, person time).

11. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

12. 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 withdraw the application. If you do not take any of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). A resubmission must fully address all the deficiencies listed, and will start a new review cycle. A partial response to this letter may not be reviewed and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss the steps necessary for approval. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry on *Formal Meetings With Sponsors and Applicants for PDUFA Products,* February, 2000 (http://www.fda.gov/cder/guidance/2125fnl.htm).

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, call Monica Hughes, M.S., Lead Regulatory Health Project Manager, at (301) 796-2320.

Sincerely,

Patricia Keegan

Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

21 Page(s) of Draft Labeling has been Withheld in Full immediately following this page as B4 (CCI/TS)