DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Our STN: BL 103234/5199

APPROVAL
February 16, 2010

Amgen, Incorporated
Attention: Annie Dang
Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320

Dear Ms. Dang:

Please refer to your supplement to your biologics license application (BLA), dated August 20, 2008, received August 21, 2008, submitted under section 351 of the Public Health Service Act for Epogen®/Procrit® (epoetin alfa).

We acknowledge receipt of your amendments dated October 15, 2008, January 23, 2009, January 28, 2009, February 20, 2009, March 2, 2009, May 1, 2009, May 20, 2009, May 28, 2009, July 27, 2009, September 8, 2009, November 5, 2009, December 8, 2009, December 18, 2009, January 15, 2010, January 21, 2010, January 25, 2010, February 1, 2010 and February 4, 2010.

Reference is made to our April 22, 2008, letter notifying you that, under Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA), a Risk Evaluation and Mitigation Strategy (REMS) is required to ensure the benefits of Epogen/Procrit (epoetin alfa) outweigh the risks.

Your request to supplement your BLA for Epogen/Procrit to revise the labeling, including the Medication Guide, and to propose a REMS has been approved.

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 Epogen®/Procrit® (epoetin alfa) were approved on July 19, 2002, for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy, we have become aware of eight controlled clinical studies that provide evidence of increased mortality and/or poorer tumor outcomes when erythropoeisis stimulating agents (ESAs) are given to patients receiving treatment for head and neck cancer, breast cancer, non-small cell lung cancer, or cervical cancer and in anemic cancer patients receiving no active anti-cancer therapy. This information was not available when Epogen®/Procrit® (epoetin alfa) was granted marketing authorization for the treatment of

anemia in cancer patients receiving chemotherapy. Therefore, we consider this information to be "new safety information" as defined in section 505-1(b) of the FDCA.

Pursuant to 505-1(f)(1), we have determined that elements necessary to assure safe use are required as part of the REMS to mitigate the risk of decreased survival and/or the increased risk of tumor progression or recurrence. The elements to assure safe use will help to achieve the following goals:

- Informed decisions between patients and their healthcare providers (HCPs) who are considering treatment with Epogen/Procrit (epoetin alfa) by educating them on the risks of Epogen/Procrit (epoetin alfa).

- Mitigation of the risk of decreased survival and/or poorer tumor outcomes in patients with cancer, as implemented through the ESA APPRISE (Assisting Providers and cancer Patients with Risk Information for the Safe use of ESAs) Oncology Program.

Your proposed REMS, submitted on January 29, 2010, and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include but is not limited to the following:

1. Assess compliance with the APPRISE Oncology Program Enrollment Requirements:
    a. An assessment of prescriber certification statistics including the number and percentage of Healthcare Providers (HCPs) actively prescribing Epogen/Procrit for cancer, by setting (private practice and hospitals), who have undergone training and have enrolled in the ESA APPRISE Oncology Program during the reporting period and cumulatively.
    b. An assessment of the hospital certification statistics including the number and percentage of institutions who order ESAs that have enrolled in the ESA APPRISE Oncology Program during the reporting period and cumulatively.
    c. Results of hospital audits including:
        i. The number of ESA prescribers who prescribe ESAs for cancer patients in comparison to the documentation maintained by the hospitals of ESA prescribers that are certified.
        ii. The number of patient-HCP signed Acknowledgement forms retained by the hospital compared to the number of patients initiating a new course of ESA therapy.
        iii. An evaluation of the reasons for hospital noncompliance with the program requirements.
        iv. A report on corrective actions taken to address noncompliance by site.
    d. A report on compliance with documentation of risk/benefit discussion and completion of ESA APPRISE Oncology Program Patient and Healthcare Professional Acknowledgement Form (i.e., the number of forms returned compared to the number of new patients initiating a new course of ESA therapy).
    e. Results of audits of private practice clinics including:
        i. The number of ESA prescribers who prescribe ESAs compared to those that are certified.

ii. The number of patient-HCP signed Acknowledgement Forms returned compared to the number of patients initiating a new course of ESA.
iii. A report on failures to adhere to certification/enrollment requirements by site.
iv. An evaluation of the reasons for noncompliance with enrollment requirements.
v. A report on corrective actions taken to address noncompliance by site.

2. Evaluate patients' understanding of the serious risks of Epogen/Procrit.

3. Report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.

4. Report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

5. Provide results of baseline and follow-up surveys of prescribers understanding of the serious risks of Epogen/Procrit, safe use conditions, and requirements of ESA APPRISE Oncology Program.

6. Evaluate Epogen/Procrit utilization patterns including the following:
   a. Hemoglobin levels in association with ongoing Epogen/Procrit therapy.
   b. Rates of Epogen/Procrit cessation following cessation of chemotherapy.
   c. Concomitant prescribing of Epogen/Procrit and myelosuppressive chemotherapy.

The methodology for how the third party vendor has conducted the assessment and collected the above described information should be submitted with the REMS Assessment.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(A), an assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and the annual progress report of postmarketing studies under 21 CFR 601.70 and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

STN BL 103234 REMS ASSESSMENT

NEW SUPPLEMENT FOR STN BL 103234
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR STN BL 103234
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this BLA and to the following address:

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

CONTENT OF LABELING

Within 14 days of the date of this letter, submit 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 that is identical in content to the enclosed labeling text. The content of labeling should be submitted by updating your applications by referencing the SPL file submitted to the drug establishment registration and drug listing system. To do this, place a link in your application submissions that directs FDA to your SPL file. For administrative purposes, please designate this submission "**Product Correspondence – Final SPL for approved BLA STN 103234/5199.**" In addition, within 14 days of the date of this letter, amend any pending supplements for this BLA with content of labeling in SPL format to include the changes approved in this supplement. For additional information on submitting labeling to drug establishment registration and drug listing and to applications, see the FDA guidances at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072339.pdf and http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

PROMOTIONAL MATERIALS

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information 21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4) to the following address or by facsimile at 301-847-8444:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

In addition, as required under 21 CFR 601.12(f)(4), you must submit your updated final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA-2253, directly to the above address. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

For information regarding therapeutic biological products, including the addresses for submissions, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/default.htm

This information will be included in your biologics license application file.

If you have any questions, call Raymond Chiang, MS, Regulatory Project Manager, at (301) 796-2320.

Sincerely,

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

Enclosures:

- Final Printed Labeling
- Medication Guide
- REMS Concise Template
- ESA APPRISE Oncology Program Enrollment Forms for Healthcare Providers
- ESA APPRISE Oncology Program Enrollment Forms for Hospitals
- ESA APPRISE Oncology Program Patient and Healthcare Professional (HCP)Acknowledgement Form
- ESA APPRISE Oncology Program Training Module for Healthcare Providers
- ESA APPRISE Oncology Program Training Module for Hospital Designees
- HCP Program Starter Kit
- ESA REMS Flashcard
- ESA APPRISE Oncology Program for Healthcare Provider Flashcard
- ESA APPRISE Oncology Program Hospital Process Overview Flashcard
- Nephrology Professional Society Letter
- Oncology Professional Society Letter
- Dear Healthcare Provider Letter to Healthcare Provider (DHCP) who may purchase or prescribe ESAs for patients with cancer
- Dear Healthcare Provider Letter to hospital Directors of Pharmacy/Administrators
- ESA APPRISE Oncology Program Website screenshots