DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 103234/5190

COMPLETE RESPONSE AND SAFETY LABELING CHANGE ORDER

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

Dear Mr. Storm:

This letter is in regard to the above referenced supplement to your biologics license application, dated May 22, 2008, received May 23, 2008, submitted under section 351 of the Public Health Service Act for epoetin alfa (Epogen/Procrit).

On April 22, 2008, we sent a letter invoking our authority under section 505(o)(4) of the Federal Food, Drug and Cosmetic Act (FDCA) to require safety related label changes to the labeling of epoetin alfa (Epogen/Procrit) to address the risk 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. The decision to require safety labeling changes was based on all available relevant information, including the recommendation of the Oncologic Drugs Advisory Committee that considered new safety information developed after Epogen/Procrit was approved.

You were directed to submit a prior-approval supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

On May 22, 2008, you submitted the prior-approval supplement containing your proposed safety related labeling changes. We promptly reviewed the prior approval supplement that included numerous versions of your labeling (e.g., 2 "patient instructions for use" (1 for Epogen and 1 for Procrit) and 41 different types of carton and vial labels (21 for Epogen and 20 for Procrit)) associated with the various formulations and presentations for Epogen/Procrit and discussed the proposed changes with you on June 19, 2008. [redacted]

In a letter dated June 27, 2008, we informed you that we had granted you an extension of the original 30-day discussion period. We determined that an extension was warranted to allow us to reach agreement with you on the content of the labeling. We indicated that all labeling discussions must be completed and your final proposal for Epogen/Procrit labeling must be received by FDA by noon EDST on July 15, 2008, as an amendment to this supplement. We received your submission in response to this letter on July 15, 2008. Please refer to the correspondence of these dates for additional information.

We have completed the review of your supplement. Our review finds that we have reached agreement on your proposed changes to the Medication Guide, Patient Instructions for Use, and Package Insert except with regard to two issues described in more detail below. We cannot grant final approval because your proposed labeling changes do not adequately address the new safety information regarding the risk of increased mortality and/or poorer tumor outcomes when ESAs are given to patients receiving treatment for certain types of cancer.

Under the authority of section 505(o)(4)(E) of the FDCA, we are ordering you to make all of the changes in the labeling listed in Attachment A. A supplement containing all of the changes to the labeling of the above-named product that are identified in Attachment A must be received by FDA by August 14, 2008. This attachment includes all changes previously proposed in your supplement STN BL 103234/5190 on which we have reached agreement and the changes identified below.

1. In the Boxed Warnings and Indications and Usage sections, replace the statement, "When the anticipated outcome of myelosuppressive chemotherapy is cure, Epogen/Procrit® is only indicated for treatment of anemia when red blood cell transfusion is not a treatment option" with "Epogen/Procrit® is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure."

2. Remove the following qualifying phrases (in italics) from the Dosage and Administration: Cancer Patients Receiving Chemotherapy subsection:

    a. Therapy should not be initiated at hemoglobin levels ≥ 10 g/dL, *except where the patient is unable to tolerate this degree of anemia due to co-morbid conditions.*

    b. Withhold Dose if: Hemoglobin exceeds a level needed to avoid transfusion *or exceeds 12 g/dL*.

We have determined that the foregoing changes are necessary for the following reasons:

Your proposed wording in item 1 above is misleading because it suggests that you have been granted an indication for treatment of anemia in patients receiving myelosuppressive chemotherapy for cancers in which cure is anticipated. Clinical studies supporting the approval of Epogen/Procrit were conducted in patients with metastatic disease without the potential for cure. You have not submitted data establishing a favorable risk:benefit ratio in patients receiving myelosuppressive chemotherapy for cancers in which cure is anticipated. The proposed

language is also unclear in that the clinical setting where "red blood cell transfusion is not a treatment option" is not a commonly understood and accepted concept used in the practice of transfusion medicine. In discussions with an external consultant expert to the FDA, neither FDA nor the expert could identify a clinical setting in which RBC transfusions is not a treatment option. Epogen/Procrit is not indicated for the acute treatment of anemia and two to six weeks are needed to achieve the pharmacologic effect of Epogen/Procrit. This period of time would be sufficient to identify and administer RBC transfusions if needed. Further, the language ordered by FDA does not prevent or prohibit healthcare providers from prescribing Epogen/Procrit in the setting where the anticipated outcome is cure under the practice of medicine.

With regard to item 2 above, your proposed inclusion of the qualifying language to the instructions in the Dosage and Administration section is unacceptable because it undermines other components of the dosing directions which instruct healthcare providers to maintain the lowest hemoglobin necessary to avoid RBC transfusions. You have not identified co-morbid conditions in which maintenance of hemoglobin levels of 10.0-12.0 g/dL results in improved survival or decreased serious morbidity. Data from randomized clinical trials indicate that maintaining higher hemoglobin levels in certain patients does not improve survival and may be harmful. For example, randomized, controlled trials of adult and pediatric patients in intensive care units have not shown a benefit to maintaining higher hemoglobin levels (e.g., 10.0 -12.0 g/dL) as compared to lower levels (e.g., 7.0 – 9.0 g/dL). Adults randomized to the lower transfusion trigger (7.0 vs. 10.0 g/dL) group experienced numerically lower 30-day mortality (Hebert, PC; Wells, G; Blaichman, MA; et al. A Multicenter, Randomized, Controlled Clinical Trial of Transfusion Requirements in Critical Care. N Engl J Med 1999; 340: 409-417). In the randomized trial conducted in patients with active cardiovascular disease and chronic renal failure, a dosing strategy seeking to maintain higher hemoglobin levels resulted in inferior survival compared with a more conservative approach(Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med 1998; 339:584-590). You have not provided evidence from studies in patients with specified co-morbid conditions, who are also receiving myelosuppressive therapy, that demonstrate that the benefits outweigh the risks for an alternate treatment strategy in which Epogen/Procrit is initiated at a hemoglobin level of 10 g/dL or higher and maintained at a higher hemoglobin level above that needed to avoid transfusions. The absence of these qualifying statements does not prohibit or prevent a healthcare provider from prescribing an alternate dosing regimen under the practice of medicine.

Pursuant to section 505(o)(4)(E), by August 14, 2008, the FDA must receive your new supplement with these changes. When we receive the required supplement, we will consider your supplement STN BL 103234/5190 to be withdrawn. Alternatively, by August 4, 2008, you may appeal this Order using the Agency's established formal dispute resolution process as described in 21 CFR 10.75. Please submit the appeal as a correspondence to your BLA. Identify the submission as FORMAL DISPUTE RESOLUTION REQUEST. A copy of the submission should be sent to:

Kim Colangelo
Associate Director for Regulatory Affairs
Food and Drug Administration
Office of New Drugs
Building 22, Room 6300
10903 New Hampshire Avenue
Silver Spring, MD 20993

Refer to the Guidance for Industry, "Formal Dispute Resolution: Appeals Above the Division Level" for further instruction regarding the content and format of your request. Questions regarding the formal dispute resolution process may be directed to Kim Colangelo at (301)796-0140. Appeals received by the Agency later than August 4, 2008 will not be entertained.

Failure to respond to this Order within the specified timeframes is a violation of section 505(o)(4) of the FDCA and could subject you to civil monetary penalties under section 303(f)(4) of the FDCA, 21 U.S.C. 333(f)(4) in the amount of up to $250,000 per violation, with additional penalties if the violation continues uncorrected. Further, such a violation would cause your product to be misbranded under section 502(z) of the Act, 21 U.S.C. 352(z), which could subject you to additional enforcement actions, including but not limited to seizure of your product and injunction.

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

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

Sincerely,

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosures:

Attachment A: Redlined Package Insert (Epogen and Procrit)
Attachment B: Medication Guide (Epogen and Procrit)
Patients Instructions for Use (Epogen and Procrit)
Carton and Vial Labeling (Epogen and Procrit)