

## Violative Advertising and Promotional Labeling Letter Epoetin alfa, Procrit (Amgen, Inc)

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June 20, 2003

Leah Palmer, Pharm. D.  
Director, Regulatory Affairs  
Amgen, Inc.  
One Amgen Center Drive  
Thousand Oaks, California 91320-1799

Dear Dr. Palmer:

This letter notifies Amgen, Inc. ("Amgen"), and by copy, Ortho-Biotech ("Ortho") that through routine monitoring and surveillance, the Advertising and Promotional Labeling Branch (APLB) in the Food and Drug Administration's Center for Biologics Evaluation and Research (CBER) has identified promotional materials for the product, Procrit (Epoetin alfa), that violate the Federal Food, Drug, and Cosmetic Act ("Act") and its implementing regulations. As we understand it, while Amgen is the manufacturer of and license holder for Epoetin alfa, it has entered into a distribution agreement with Ortho, which markets Epoetin alfa under the trade name Procrit for certain indications. APLB has reviewed numerous advertising and promotional labeling items, including an advertisement for Cancer Management Handbook (MIN X1082) (copy enclosed).

### **Promotion of Misleading and Unsubstantiated Claims**

1. Promotional materials are misleading if they contain a representation or suggestion, not approved or permitted for use in the labeling, that a drug is better, more effective, or is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience, 21 CFR § 202.1 (e)(6)(i).

Your Cancer Management Handbook advertisement is misleading because it presents claims that, to the best of FDA's knowledge, are not supported by substantial evidence or substantial clinical experience. This ad claims, in a very prominent, bold header that, "With Procrit, help get his Hb BACK TO NORMAL\*." This message, particularly in the context of the immediately accompanying language, "Procrit provides...", represents that Procrit will return hemoglobin (Hb) levels back to normal in chemotherapy patients. This claim is misleading because it implies that healthcare professionals should treat patients suffering from chemotherapy-induced anemia with Procrit to bring their hemoglobin to a truly normal range: 13.5 to 18 g/dL for males and 12 to 16 g/dL for females. The asterisked note stating, "\*Target Hb range 12 to 13 g/dL," near the bottom of the page against a blue background on the far left is extremely

small, difficult to find, and inadequate to fairly balance the overwhelming impression that Procrit should be dosed to achieve hemoglobins in a normal range, instead of the stated target range of 12 to 13 g/dL.

In addition, the prominent claim, "...BACK TO NORMAL," misleadingly implies that dosing and administration of Procrit should be continued until Hb levels reach a normal range (13.5 to 18 g/dL for males and 12 to 16 g/dL for females). Please note that the approved package insert (PI) clearly states that, "If the hematocrit exceeds 40%, the dose of Procrit should be withheld until the hematocrit falls to 36%."

Procrit does not have an approved indication for the attainment of "normal" hemoglobin. The Agency has not reviewed, nor is it aware of, any data that addresses a clinical benefit that would accrue to the attainment of "normal" hemoglobin per se. Clinical studies with Procrit therapy in certain cancer patients on chemotherapy showed an increased hematocrit response rather than achievement of "normal" hemoglobin.

If there are data to address a clinical benefit that would accrue to the attainment of "normal" hemoglobin, please submit it within 30 days of the date of this letter for FDA review. In the absence of such data, you should immediately cease any further dissemination of all advertising and promotional materials that contain these claims and similar presentations and revise them to ensure that your claims are clearly set forth with text, if necessary, in equal prominence and directly connected to the claim.

2. Promotional materials may be false or misleading if they contain favorable information or conclusions from a study that is inadequate in design, scope, or conduct to furnish significant support for such information or conclusions, 21 CFR § 202.1 (e)(7)(i).

The same revised advertisement includes a prominent bold header statement, "*Timely & Significant Hb Response\**" with three references promoting the following claims:

PROCRIT provides:

- *Timely*  $\geq 1$  g/dL hemoglobin (Hb) increase in **4 weeks**<sup>1-3</sup>
- *Timely & Significant* approximately 2 g/dL Hb increase **in as early as 8 weeks**<sup>2,3</sup>

Under this claim you presented a graph, titled "Procrit—Timing is Everything," to show the Hb response from baseline to 4 weeks (timely response), 8 weeks (significant response), 12 weeks, and 16 weeks (sustained response). The legend on the graph notes "Glaspy et al (n=2030), Demetri et al (n=2289)", and the

asterisked note stating “Data from 2 large nonrandomized, multicenter trials of over 4000 anemic cancer patients receiving chemotherapy.”

However, both the claim and graph are misleading, because they imply that Procrit is more effective with faster Hb response than has been demonstrated by substantial evidence or substantial clinical experience. As reported in the cited reference, Glaspy et al, in an open-label study: “Of the 2,030 patients, 1,047 (52%) completed the 4-month study” [of epoetin alfa (Procrit) therapy]. Of these 1,047 patients, 233 received one or more transfusions during epoetin alfa therapy. It is well known that red blood cell (RBC) transfusions impact Hb levels more quickly than treatment with epoetin alfa. The claim does not include critical information such as whether Hb values from patients who have received RBC transfusions have or have not been included in the mean change in Hb analysis and whether the “early responder” patient population is from a subset analysis. In addition, the claims of “timely” and “significant” are unsupported by these data since they were from an open-label study with no comparative treatment arm from which claims of timeliness or statistical significance can be generated.

The graph also misleadingly implies that all patients in the Glaspy and Demetri articles completed 16 weeks of therapy when, in fact, only 1,047 (52%) and 1,286 (56%), respectively, completed 16 weeks of therapy.

You should immediately cease any further dissemination of all advertising and promotional materials that contain these claims and similar presentations.

This letter is not intended to be an all-inclusive list of deficiencies associated with your promotion of the above product. It is your responsibility to ensure that all materials distributed within the United States are in conformance with each requirement of the Act and applicable regulations.

You should respond within ten days of the date of this letter. Your response should include a statement of your intent to comply with each of the above, a list of all similarly violative materials, a description of the method for discontinuation, and the discontinuation date.

Your response should be directed to Mr. Glenn N. Byrd, Chief, APLB, at the address listed below. Should you have any questions or concerns involving this matter, please contact Mr. Byrd at 301-827-3028.

Center for Biologics Evaluation and Research  
Office of Compliance and Biologics Quality  
Division of Case Management  
Advertising and Promotional Labeling Branch, HFM-602  
1401 Rockville Pike  
Rockville, MD 20852-1448

Sincerely,

----- *signature* -----

Mary A. Malarkey  
Director, Division of Case Management  
Office of Compliance and Biologics Quality  
Center for Biologics Evaluation and Research

Enclosures

cc: Ortho Biotech, Inc. (w/ Encs)