



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

STN BL 103951/5248
STN BL 103234/5256

SUPPLEMENT BLA APPROVAL
June 24, 2011

Amgen
Attention: Ravi Magavi, M.S.
Senior Manager, Regulatory
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. Magavi:

Please refer to your Supplemental Biologics License Applications (sBLA), dated August 10, 2010, received August 11, 2010, submitted under section 351 of the Public Health Service Act for Aranesp[®] (Darbepoetin alfa) and Epogen[®]/PROCRI[®] (Epoetin alfa).

The April 22, 2011 and June 20, 2011, submissions constituted a complete response to our February 10, 2011, action letters.

These "Prior Approval" labeling supplements to your biologics license applications propose the following change(s): Labeling revision to (1) Indication and Usage, (2) Warnings, (3) Adverse Reactions, (4) Dosage and Administration, and (5) Clinical Study sections of the Aranesp[®] (Darbepoetin alfa) and Epogen[®]/PROCRI[®] (Epoetin alfa) United States Prescribing Information (USPI).

Your approved Medication Guide is part of the risk evaluation and mitigation strategy (REMS) approved in supplements BLA 103951/5173 and BLA 103234/5166.

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the 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 to the enclosed labeling (text for the package insert, and Medication Guide) and include the labeling changes proposed in any pending “Changes Being Effected” (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>. For administrative purposes, please designate this submission “**Product Correspondence – Final SPL for approved BLA STN 103951/5248 and 103234/5256.**”

Also within 14 days, amend all pending supplemental applications for this BLA, including pending “Changes Being Effected” (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

The SPL will be accessible via publicly available labeling repositories.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Aranesp[®] (Darbepoetin alfa) and Epogen[®]/PROCRIT[®] (Epoetin alfa) were approved on September 17, 2001 and on June 1, 1989, respectively, we have become aware of the TREAT trial results. In the TREAT trial, the dose-schedule of Aranesp[®] (Darbepoetin alfa) administered in the Aranesp[®] treatment arm was shown to result in an inferior safety outcome when compared to the control arm therapy of Aranesp[®] given once monthly at a dose of 0.45 µg/kg only during intervals when the hemoglobin (Hb) level was below 9 g/dL. The Aranesp[®] dosing strategy in the Aranesp[®] treatment arm produced hemoglobin levels greater than the target level and substantially greater than current transfusion thresholds. Among patients with a prior history of stroke receiving Aranesp[®] on the treatment arm, stroke occurred in 12% of patients (27/231), an annualized incidence of 5.3% versus 1.9% on the control arm. Among patients with a prior history of malignancy, deaths due to all causes and deaths due to malignancy were higher on the Aranesp[®] (Darbepoetin alfa) treatment arm compared to the control arm.

In addition, during our review of the TREAT trial, FDA re-analyzed the primary outcomes of the prior controlled trials of ESA therapy in chronic kidney disease (CKD) and identified increased risks of adverse cardiovascular outcome and death when compared to previously published reports.

We consider this information to be “new safety information” as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risks of adverse cardiovascular reactions and death.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious risks of adverse cardiovascular reactions and death.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1. In patients with CKD on dialysis, conduct one or more trials to identify an optimal strategy of ESA dose and schedule. These trials should identify the optimal dosing strategy which will demonstrate the superiority of the ESA dosing strategy to minimize hemoglobin (Hb) variability, excursions, rate of change of Hb, and explore providing symptom benefit.
2. In patients with CKD who are not on dialysis (NOD), conduct one or more trials to determine whether a dosing strategy (e.g. fixed dose strategy) different from that in the approved labeling can further reduce exposure to ESA while preserving the benefit of reducing transfusion use.

Submit timetables for final protocol submission, trial completion, and submission of final report for the postmarketing requirements described above within 30 days from the date of this letter.

Submit the protocols to your INDs 7413 and 2265, with a cross-reference letter to these BLAs. Submit all final reports to your BLA. Prominently identify submissions with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a

safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

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

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. 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>.

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 address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Ebla Ali Ibrahim, Senior Regulatory Health Project Manager, at (301) 796-3691.

Sincerely,



/Robert C. Kane/
Robert C. Kane, MD
Acting Deputy Director for Safety
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research



/Ann T. Farrell/
Ann T. Farrell, M.D.
Acting Division Director
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling
REMS – Medication Guide