



BLA 103951/5173 & 103951/5258

SUPPLEMENT BLA APPROVAL

June 24, 2011

Amgen Incorporated
Attention: Elizabeth Williams, M.S., RAC
Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop: 17-2-B
Thousand Oaks, CA 91320-1799

Dear Ms. Williams:

Please refer to your Supplemental Biologics License Application (sBLA) 103951/5173, dated December 20, 2007, received December 26, 2007, and to your sBLA 103951/5258 dated October 14, 2010, received October 15, 2010, submitted under section 351 of the Public Health Service Act for Aranesp[®] (darbepoetin alfa).

Supplement 103951/5173

Supplement 103951/5173 proposes to amend your BLA for Aranesp with the following:

1. Final reports, datasets, and results of analyses for multiple studies/clinical trials submitted to address items 3, 4, and 5 of our May 31, 2007, supplement request letter regarding advice provided during the May 10, 2007, Oncologic Drugs Advisory Committee (ODAC) meeting.
2. A revised package insert to conform to the labeling content and format requirements specified in 21 CFR 201.56(d) and 201.57.
3. Modifications to the approved risk evaluation and mitigation strategy (REMS) that include an updated Medication Guide and updated appended REMS documents to provide consistency with the revised package insert.

We acknowledge receipt of your amendments dated through June 21, 2011.

The March 22, 2011, submission constituted a complete response to our April 27, 2010, action letter.

Supplement 103951/5258

Supplement 103951/5258 proposes to revise the ESA APPRISE Oncology Program REMS document and the REMS materials, including the REMS website, to facilitate implementation of the program and to more concisely and effectively present important information.

We acknowledge receipt of your amendments dated through June 21, 2011.

In addition, we acknowledge receipt of your most recent REMS assessment dated February 16, 2011, submitted under STN 103951/5268. We have found the REMS assessment to be complete.

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.

In addition, the attached labeling contains additional revisions to the package insert and REMS (i.e., Medication Guide) that derive from CDER's review of the "Trial to Reduce Cardiovascular Events with Aranesp Therapy" (TREAT) conducted in the chronic renal failure patient population and submitted under sBLA 103951/5248.

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, patient instructions for use, 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 103951/5173.**"

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.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

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.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Aranesp[®] (darbepoetin 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. Your proposed modifications to the REMS consist of revisions to the REMS document, Medication Guide, and appended REMS materials. These modifications are to provide consistency with the revised package insert and to revise the REMS document and the ESA APPRISE Oncology Program REMS materials, including the REMS website, to facilitate implementation of the program and to more concisely and effectively present important information.

Your proposed modified REMS, submitted on March 22, 2011 (sBLA 103951/5173) and March 23, 2011 (sBLA 103951/5258), as amended, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS will remain the same as that approved on February 16, 2010.

There are no changes to the REMS assessment plan described in our February 16, 2010, letter.

We remind you that 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.

We also remind you that 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. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. 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 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.

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:

BLA 103951 REMS ASSESSMENT

**NEW SUPPLEMENT FOR BLA 103951
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 103951
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

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

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

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 Dr. 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:

- Content of Labeling
- Instructions For Use
- 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
- Dear Healthcare Provider Letter to Healthcare Providers (DHCP) who prescribe or prescribe and dispense ESAs for patients with cancer

- Dear Director of Pharmacy/Administrator Letter to hospitals that dispense ESAs for patients with cancer
- ESA APPRISE Oncology Program Website screenshots
- Guidelines for PAF Integration within Healthcare Systems and Clinics