DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 103951/S-5375

SUPPLEMENT APPROVAL
RELEASE REMS REQUIREMENT

Amgen, Inc.
Attention: Melissa Westenburg, PharmD.
Manager, Regulatory Affairs
One Amgen Center Drive, Mail Stop: 17-2-B
Thousand Oaks, CA 91320-1799

Dear Dr. Westenburg:

Please refer to your Supplemental Biologics License Application (sBLA), dated March 17, 2017, received March 17, 2017, and your amendment, submitted under section 351(a) of the Public Health Service Act for Aranesp® (darbepoetin alfa) Injection: 25 mcg, 40 mcg, 60 mcg, 100 mcg, 200 mcg, 300 mcg, and 500 mcg/1 mL, and 150 mcg/0.75 mL single dose vials, 10 mcg/0.4 mL, 25 mcg/0.42 mL, 40 mcg/0.4 mL, 60 mcg/0.3 mL, 100 mcg/0.5 mL, 150 mcg/0.3 mL, 200 mcg/0.4 mL, 300 mcg/0.6 mL, and 500 mcg/1 mL single-dose prefilled syringes.

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated February 16, 2016, and refer to our REMS Modification Notification letter dated March 7, 2017.

This Prior Approval supplemental biologics application provides for (1) revisions to the Warnings and Precautions section of the Aranesp (darbepoetin alfa) prescribing information based on completed clinical trial EPO-ANE-3010 entitled "*A Randomized, Open-Label, Multicenter, Phase 3 Study of Epoetin Alfa plus Standard Supportive Care versus Standard Supportive Care in Anemic Patients With Metastatic Breast Cancer Receiving Standard Chemotherapy*," and (2) elimination of the requirement for the approved Aranesp (darbepoetin alfa) REMS.

APPROVAL & LABELING

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.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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 prescribing information, 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.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes 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.

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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

PMC 3198-1 Submit periodic reports based on review of relevant data from available sources, including US electronic medical records and claims databases, to assess the

utilization of Epogen, Procrit and Aranesp for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.

The periodic reports should include: (a) proportion of patients with cancer receiving chemotherapy who also receive concomitant Epogen/Procrit or Aranesp, (b) analysis of hemoglobin levels at baseline upon initiation of Epogen/Procrit or Aranesp, and (c) subgroup analysis according to the following cancer types: metastatic breast cancer, adjuvant therapy for breast cancer, non-small cell lung cancer, colorectal cancer, and lymphoma.

The timetable you submitted on March 31, 2017 states that you will conduct this study according to the following schedule:

Draft Protocol (Analysis Plan) Submission: 05/2017
Final Protocol (Analysis Plan) Submission: 08/2017
Interim Report Submissions:
Baseline data Report Submission (2014-2016 data): 03/2018
Interim Report Submission (2017 data): 01/2019
Interim Report Submission (2018 data): 01/2020
Interim Report Submission (2019 data): 01/2021
Interim Report Submission (2020 data): 01/2022
Study Completion (data lock): 10/2022
Final Report Submission: 01/2023

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

Submit all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Aranesp (darbepoetin alfa) was originally approved on February 16, 2010, and the most recent modification was approved on December 31, 2013. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of

assessments of the REMS. As communicated in the March 7, 2017 REMS Modification Notification Letter, we determined that the elements to assure safe use are no longer necessary to ensure the benefits of Aranesp (darbepoetin alfa) outweigh the risks and that the approved REMS for Aranesp (darbepoetin alfa) had to be modified to minimize the burden on the healthcare delivery system of complying with the REMS.

We have determined that elements to assure safe use are no longer necessary to ensure the benefits of Aranesp (darbepoetin alfa) outweigh its risks because the REMS assessments have indicated that healthcare providers demonstrate acceptable knowledge of the product risks of decreased survival and/or the increased risk of tumor progression or recurrence, and that product utilization analyses show that recent and current prescribing use is consistent with the labeled indication.

The products' risks can be conveyed adequately via the current product labeling. The Medication Guide will continue to be part of the approved labeling.

Therefore, because the elements to assure safe use are no longer necessary to ensure the benefits of the drug outweigh the risks, a REMS is no longer required for Aranesp (darbepoetin alfa).

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 prescribing information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the prescribing information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), 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, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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 Ms. Diane Leaman, Regulatory Project Manager, at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Barry W. Miller
Acting Deputy Director for Safety
Division of Hematology Products
Office of Hematology Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BARRY W MILLER
04/13/2017