Division Director Summary Review

Date	June 24, 2011
From	Patricia Keegan, M.D.
Subject	Division Director Summary Review
BLASupplement #	STN BL 103951/5173
Applicant Name	Amgen, Inc.
Date of Submission	December 26, 2007
Date of CR letter	October 24, 2008
Date of Resubmission	October 26, 2009
Date of CR letter	April 27, 2010
Date of Resubmission	March 22, 2011
PDUFA Goal Date	May 23, 2011
Proprietary Names / Established (USAN) Name	Aranesp® darbepoetin alfa
Dosage Forms / Strength	Solution ([b) (4)] polysorbate buffer solutions) for subcutaneous or intravenous injection in single-use vials or prefilled syringes. Strengths range from 25 mcg to 300 mcg for vials and 25 mcg to 500 mcg for prefilled syringes
Current Indication(s)	1. Aranesp is indicated for the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and patients not on dialysis. 2. Aranesp is indicated 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. 3. Limitations of use: Aranesp has not been shown to improve quality of life, fatigue, or patient well-being. Aranesp is not indicated for use: • In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy. • In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure. • As a substitute for RBC transfusions in patients who require immediate correction of anemia *[see Clinical Pharmacology (12.2)]*.
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Project manager generated minutes & reviews	Monica L. Hughes Mona Patel
Medical Officer Reviews	Chaohong Fan Kaushik Shastri Minh-Ha Tranh Saleh Ayache
Deputy Director for Safety Review	Jeff Summers
Statistical Reviews	Yuan-Li Shen Mark Rothmann
Pharmacology Toxicology Reviews	Andrew McDougal Anne Pilaro Yanli Ouyang
OBP Reviews	Ingrid Markovic Kimberly Rains
Clinical Pharmacology Review	Aakansha Khandelwal
Division of Risk Management Review	Melissa Huett Sharon Mills Amarylis Vega
DDMAC, SEALD team Review	Iris Massucci
DDMAC reviews	Cynthia Collins Michelle Safarik Carole Broadnax
Pediatric and Maternal Health Staff Review	Jeanine Best Richard Araojo

OND=Office of New Drugs
OBP=Office of Biotechnology Products
DDMAC=Division of Drug Marketing, Advertising and Communication
SEALD=Study Endpoints and Labeling Development
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK=Division of Risk Management

Division Director Summary Review

1. Introduction

This efficacy supplement was received on December 26, 2007 as one of two supplements responding to FDA's supplement request letter of May 31, 2007. This supplement was subsequently unbundled with review of information responding to the May 31, 2007 letter conducted under BL STN 103951/5173, and review of proposed labeling changes to the Warnings and Precautions section describing the overall survival and progression-free survival results of Study 20010145, which were considered to be new claims rather than new safety information, conducted under the unbundled supplement, identified as BL STN 103951/5175, the subject of a separate review. The May 31, 2007 letter made specific requests for revision to product labeling to enhance safe and effective use of Aranesp for the treatment of anemia due to concomitant cancer chemotherapy. These specific requests were based on the results of six multicenter, randomized trials assessing the effect of ESAs in patients with cancer that demonstrated or suggested harmful effects (decreased survival or more rapid tumor progression/recurrence). The requested labeling changes were consistent with the recommendations from the May 10, 2007 Oncologic Drugs Advisory Committee (ODAC) meeting at which the results of these studies were presented and discussed.

Amgen provided revised labeling in response to FDA's May 31, 2007 letter under two separate supplements, a "Changes Being Effected" labeling supplement (STN BL 103951/5164) addressing items 1, 2, and 6 of the May 31, 2007, letter which was approved November 8, 2007 and the "Prior Approval Supplement" (STN BL 103951/5173), which is the subject of this review, responding to items 3, 4, and 5 of the May 31, 2007 letter. The PAS submission contains clinical study reports and an integrated dataset containing data from datasets from eleven randomized, placebo-controlled studies of darbepoetin alfa (Aranesp) in patients with anemia and non-myeloid malignancy receiving chemotherapy (20010119, 980291 schedule 1, 980291 schedule 2, 990114, 980297, 20000161, 20010103, 20010145, 20020149, 20030204, 20030232), additional analyses, and proposed labeling changes. In addition, as discussed at the July 25, 2007 meeting with Amgen, the proposed labeling provided in this submission was reformatted for consistency with the Physician's Labeling Rule (PLR). Amgen stated that the focus of the PLR conversion was made with "attention to the format, reduction of repetition and modification of the Adverse Reaction section of the PI".

The review of this application was coordinated across the Division of Biologic Oncology Products and the Division of Medical Imaging and Hematology Products. The medical oncology reviewers and supporting statistical reviewers in the Division of Biometrics V evaluated the responses to the May 31, 2007 letter and all clinical portions of product labeling for the cancer-related indication, while the review of clinical portions of product labeling for all other approved indications were conducted by reviewers in the Division of Hematology. Additional review staff, as listed above, participated in the review of product labeling changes

to conform with the requirements of 21 CFR 201.56(d) and 201.57. In addition, as appropriate, the review of the Epogen/Procrit and Aranesp labels were conducted jointly to describe class effects.

The assessment of the medical oncology reviewers and statistical reviewers, as well as secondary reviewers was that the proposed approach by Amgen to integrate data from 12 (two of these "studies" were themselves pooled data from distinctly numbered protocols of the same design) randomized, placebo-controlled studies assessing the effects of epoetin alfa and 11 randomized, placebo-controlled studies (including "continuation protocols" for two trials assessing efficacy and one protocol with two reports for Schedules 1 & 2) assessing darbepoetin alfa was not interpretable for addressing issues 3, 4, and 5 of the May 31, 2007 letter for reasons discussed below. Instead, FDA's proposed modifications to product labeling rely on a conservative approach, further refining the indications and usage sections of the Aranesp label to attempt to limit use to the population of patients with cancer who are most likely to derive benefit as well as to attempt to mitigate the risks of increased mortality and shorter time to disease progression. Labeling changes also reflect additional information and Advisory Committee advice received during the course of the supplement review. Since submission of this supplement on December 26, 2007, product labeling has been updated to include new information on the risks of pure red cell aplasia, new study results demonstrating adverse outcomes in patients with chronic renal failure and in patients with cancer, as summarized below. Based on additional study results in patients with cancer, FDA sought advice of the ODAC on March 13, 2008 which resulted in additional labeling changes, consistent with the conservative dosing recommendations mentioned above and further limiting product use. These labeling changes were made as part of FDA-ordered safety labeling changes and approved on August 5, 2008.

A complete response letter was issued on October 24, 2008, requesting additional information to support proposed labeling; the response was received on October 26, 2009 as a Class II resubmission. The review of additional clinical and non-clinical information provided in the resubmission was completed and incorporated into product labeling, however agreement on final labeling, including proposed modifications to the Medication Guide and REMS, were not reached. A complete response letter was issued on April 27, 2010.

A Class 1 resubmission containing Amgen's proposed revisions to product labeling and modifications to the REMS were submitted on March 22, 2011. The review of the materials in this supplement were coordinated with the ongoing reviews of a REMS modification submitted under STN BL 103951/5258, (b) (4) and a prior approval supplement containing the final report for the TREAT study, under STN 103951/5248. Based on agreement between FDA review staff and Amgen on final product labeling and REMS modifications, this supplement will be approved.

2. Background

Erythropoietin is a glycoprotein whose main function is to stimulate the proliferation and differentiation of erythroid precursors in the bone marrow. Erythropoietin is produced mainly in the kidneys, though several other tissues produce lesser amounts of the growth factor.

Aranesp (darbepoetin alfa) is an erythropoiesis-stimulating protein, closely related to endogenous human erythropoietin, which is produced in Chinese hamster ovary cells by recombinant DNA technology. Darbepoetin alfa is a 165-amino acid protein that differs from recombinant human erythropoietin in containing 5 N-linked oligosaccharide chains, whereas recombinant human erythropoietin contains 3 chains. The additional carbohydrate chains increase the approximate molecular weight of the glycoprotein from 30,000 to 37,000 daltons. Darbepoetin alfa has a three-fold longer terminal half-life than epoietin alfa and a five-fold lower affinity for erythropoietin receptors.

Aranesp was approved for marketing in the U.S. on September 17, 2001 for the treatment of anemia in patients with chronic renal failure based on the results of thirteen Amgen-sponsored studies, in which 2198 patients with chronic renal failure (CRF) were enrolled; in these trials, 1598 patients received ARANESP and 600 patients received epoetin alfa as an active comparator.

Aranesp was approved for "the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy" on July 19, 2002. This approval was based primarily on the results of Protocol 980297, "A Double-Blind, Placebo-Controlled, Randomized, Study of NESP for the Treatment of Anemia in Lung Cancer Receiving Multi-cycle Platinum Containing Chemotherapy". This was a multicenter, multinational study in which 320 patients were enrolled and randomized 1:1 to receive either Aranesp 2.25 μg/kg QW (treatment arm) or placebo. Eligibility criteria included lung cancer (either small cell carcinoma or non-small cell carcinoma) a cancer treatment plan of at least 12 additional weeks of platinum-containing chemotherapy, and anemia (hemoglobin <11g/dl). The primary endpoint was the estimated Kaplan-Meier proportion of subjects who received RBC transfusions between week 5 and the end of the treatment phase (EOTP). Week 5 was specified since hematologic responses to Aranesp are not observed until 3-6 weeks after the initiation of therapy. The primary efficacy analysis was conducted in patients who had completed the first 4 weeks of study. In this analysis, patients who withdrew or discontinued from the study after week 4 for death or disease progression were censored, while those who withdrew for any other reason were imputed to be transfused (treatment failures for primary endpoint). A significantly lower proportion of patients in the Aranesp arm, 26% (95% CI: 20%, 33%) required transfusion compared to 60% (95% CI: 52%, 68%) in the placebo arm (Kaplan-Meier estimate of proportion; $p < 0.001$ by Cochran–Mantel-Haenszel test).

The labeling for Aranesp was expanded on March 23, 2006 to include a new dosing regimen of 500 mcg once every 3 weeks (Q3W) for the treatment of anemia in adults with non-myeloid malignancies, where anemia is due to the effect of concomitantly administered chemotherapy. The safety and effectiveness of the Q3W regimen in reducing the requirement for red blood cell (RBC) transfusions in patients undergoing chemotherapy was assessed in a randomized, double-blind, multinational study. This study was conducted in anemic (Hgb < 11 g/dL) patients with non-myeloid malignancies receiving multicycle chemotherapy. Patients were randomized to receive Aranesp at 500 mcg once every 3 weeks (n = 353) or 2.25 mcg/kg (n = 352) administered weekly as a subcutaneous injection for up to 15 weeks. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 mcg in the

once every 3 week group and 1.35 mcg/kg in the once weekly group) if hemoglobin increased by more than 1 g/dL in a 14-day period. Study drug was withheld if hemoglobin exceeded

13 g/dL. In the once every 3 week group, 254 patients (72%) required dose reductions (median time to first reduction at 6 weeks). In the once weekly group, 263 patients (75%) required dose reductions (median time to first reduction at 5 weeks).

Efficacy was determined by a comparison of the Kaplan-Meier estimates of the proportion of patients who received at least one RBC transfusion between day 29 and the end of treatment. Three hundred thirty- five patients in the once every 3 week group and 337 patients in the once weekly group remained on study through or beyond day 29 and were evaluated for efficacy. Twenty-seven percent (95% CI: 22%, 32%) of patients in the once every 3 week group and 34% (95% CI: 29%, 39%) in the weekly group required a RBC transfusion. The observed difference in the proportion of patients receiving one or more transfusions for the once every 3 week schedule as compared to the once weekly) was -6.7% (95% CI: -13.8%, 0.4%).

There are two ESAs approved for the treatment of anemia due to chemotherapy in the United States, darbepoetin alfa (Aranesp, Amgen Inc) and epoetin alfa (Procrit/ Epogen, Amgen Inc). In addition, there are several ESAs approved in other countries and for which clinical experience in patients with cancer are available. FDA considers safety information derived from any ESA as relevant for characterization of risks for the entire class. Since 1993, multiple randomized controlled clinical trials conducted in patients with cancer, which were designed to isolate the effect of the erythropoiesis-stimulating agent, demonstrated or exhibited a trend towards shorter survival and/or poorer tumor outcomes in patients receiving an ESA compared to patients receiving transfusion support alone. This information has been summarized in FDA briefing documents for Oncologic Drugs Advisory Committee meetings held May 4, 2004, May 10, 2007, and March 13, 2008. In addition, this data is summarized in Warnings section of the product labeling for Aranesp and for Epogen/Procrit.

Following the May 10, 2007 ODAC meeting at which these data were discussed, FDA issued a supplement request letter to Amgen. The letter stated that, based on discussion during the May 10, 2007 meeting, FDA requested that Amgen submit a prior approval supplement (PAS) that would include revised labeling to adequately addressing the recommendations for changes or to provide data supporting current or alternate labeling changes from those recommended during that Advisory Committee meeting. Specifically, FDA requested the following:

1. Revision of the INDICATIONS AND USAGE section, to include a statement that Epogen/Procrit is not indicated for use in patients receiving chemotherapy for any of the following primary tumor types: adenocarcinoma of the breast, squamous cell cancer of the head and neck, non-small cell lung cancer, or lymphoid malignancies.

2. Revision of the INDICATIONS AND USAGE section, to clarify the severity of anemia for which Epogen/Procrit is indication, by inclusion of the maximum (and if appropriate, minimum) pretreatment hemoglobin level.

3. Revision of the DOSAGE AND ADMINISTRATION section to specify a lower maximum hemoglobin level (i.e., hemoglobin level less than 12 g/dL) at which dosing should be suspended or terminated.

4. Revision of the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections to indicate that Epogen/Procrit should be discontinued following the completion of the concomitant chemotherapy regimen.

5. Revision of the INDICATIONS AND USAGE section to indicate that Epogen/Procrit is not indicated for use in patients who are not receiving myelosuppressive chemotherapy. This statement should include patients who are receiving no active treatment, radiotherapy treatment, and treatment with non-myelosuppressive therapy such as hormonal agents and therapeutic biologic products.

Following issuance of the May 31, 2007 letter, Amgen met with FDA on July 25, 2007 to discuss the proposed contents of the requested labeling supplement. Amgen's proposed approach was to conduct re-analyses of existing data (e.g., Cochrane analysis and inclusion of additional studies) to further evaluate the impact of ESAs on tumor progression and on survival, and to identify post-marketing studies designed to assess the safety and efficacy of ESAs when administered according to more conservative dosing regimens.

On September 7, 2007, FDA issued an additional letter requesting that Amgen make specific labeling changes in a separate "Changes Being Effected" (CBE) labeling supplement. Amgen provided responses to items 1, 2, and 6 of FDA's 31 May 2007 letters in a CBE supplement (STN BL 103951/5157) submitted on September 19, 2007. A CBE supplement (STN BL 103234/5158) was submitted for Epogen/Procrit on September 19, 2007. Both supplements were approved on November 8, 2007.

In addition to the CBE supplement discussed above, the following additional safety labeling changes have been approved since submission of STN BL 103951/5173:

- STN/BL 103951/5170: Approval on March 7, 2008 to include a Boxed Warning summarizing the risks of increased mortality and/or poorer tumor outcomes obtained in randomized studies in patients with cancer and in those with chronic renal failure and to update the Warnings section to include the results of two additional randomized, controlled studies in patients with cancer (PREPARE trial and GOG-191 trial) demonstrating adverse survival or tumor outcomes in patients with cancer receiving an ESA.
- (b) (4)
- STN 103951/5195: Approval on November 19, 2008 of a CBE supplement containing a medication guide, patient instructions for use, revised container and carton labeling and revised package insert. (b) (4)

- STN BL 103951/5211: Approval on October 13, 2009 of a CBE supplement modifying the WARNINGS section of the Package Insert to describe the potential for pure red cell aplasia (PRCA) in the specific clinical setting of hepatitis C virus (HCV) therapy with ribavirin and interferon

- STN BL 103951/5223: Approval on January 11, 2010 of CBE labeling to include the results of the TREAT study.

- STN BL 103951/5197: Approval on February 16, 2010 of a Risk Mitigation and Evaluation Strategy, to mitigate the risk of decreased survival and/or the increased risk of tumor progression or recurrence in patients with cancer for whom Aranesp is prescribed.

- STN BL 103951/5248: Prior approval supplement, submitted on August 10, 2010 and received August 11, 2010, which contained a final study report for the "Trial to Reduce Cardiovascular Events with Aranesp Therapy" (TREAT) conducted in the chronic renal failure patient population and proposed revisions to the package insert and REMS (i.e., Medication Guide) to include information on the TREAT trial. Labeling revisions based on this supplement included changes to the Indication and Usage, Warnings, Adverse Reactions, Dosage and Administration, and Clinical Experience sections of the product labeling. A complete response letter was issued February 10, 2011 and resubmission submitted April 22, 2011. Revisions to the Medication Guide based on this supplement were incorporated under the review of STN BL 103951/5173 as part of the REMS modification under this supplement. Refer to DHP reviews regarding labeling changes and REMS modifications relating to data submitted to STN BL 103951/5248.

- STN BL 103951/5258: This prior approval supplement submitted October 14, 2010 and received October 15, 2010, which contains proposals to revise the ESA APPRISE Oncology Program REMS document and the REMS materials, including the REMS website, to provide consistency with the revised package insert and to facilitate implementation of the program and to more concisely and effectively present important information.

- (b) (4)

The chronology of this submission is briefly summarized below

Dec. 20, 2007: STN BL 103234/5166 submitted (received by FDA on Dec. 26, 2007).
Feb. 1, 2008: Acknowledgment letter issued.
Feb 21, 2008: FDA notified Amgen that the supplement was filed and that preliminary deficiencies identified in the filing review would be communicated in a subsequent letter.

March 7, 2008: FDA letter issued with preliminary deficiencies regarding proposed labeling format and requested define document files for 4 protocols (20030232, 980297, 990114, and 980291 schedules 1 &2), SAS programs used to produce derived variables, and raw & derived datasets for protocol 20020149.

- April 18, 2008: Amgen submitted partial responses to the 3/7/08 letter
- May 30, 2008: Amgen submitted additional information (define.pdf file for 20020149) as responses to the 3/7/08 letter

August 19, 2008: FDA issued a letter requesting clarification of the relevance of Protocol 20010119 to the supplement and, if relevant, requesting that an individual study dataset be provided that datasets containing raw and derived variables and SAS programs be submitted to the supplement. The letter also requested additional information (e.g., final reports, case report forms, individual datasets, and requests for clarification of study conduct) for Protocols 20000161, 20010103, 980291 (schedules 1 & 2), 990114, 20030232, 980297, and 20020149.

- Sept 12, 2008: Amgen submitted partial responses to 8/19/08 letter
- Sept. 18, 2008: Amgen submitted partial responses to 8/19/08 letter
- Oct 15, 2008: Amgen submitted partial responses to 8/19/08 letter

October 24, 2008: FDA issued a complete response letter requesting the following items

- Resubmission of datasets for Protocol 990114 (also requested in 8/19/08 IR letter)
- Data (or source of data) for rat and rabbit reproductive toxicology studies in support of proposed labeling
- Response to comments requesting information contained in proposed labeling attached to the 10/24/08 CR letter
- Revised product labeling
- Updated information on world-wide safety experience

October 23, 2009: Amgen submitted a Complete Response to the Oct. 24, 2008 letter, which was received on October 26, 2009 and designated a Class 2 resubmission.

Additional amendments to this efficacy supplement received during this review cycle were submitted on November 2, 2009, January 11, 15, and 28, 2010, March 17, 22, 23, and 29, 2010, and on April 8 and 12, 2010.

April 27, 2010: A second Complete Response letter was issued due to failure to reach agreement on final labeling, including proposed changes to the Medication Guide and other modifications to the REMS.

Prior to the resubmission, FDA conducted informal labeling negotiations to resolve disagreements on product labeling.

March 22, 2011: Amgen submitted a Complete Response to the April 27, 2010, which was designated a Class 1 resubmission. The proposed labeling by Amgen that was consistent with labeling negotiated informally.

3. CMC/Device

No new CMC information was submitted in or required to complete review of this application. All CMC reviewer comments regarding the package insert (Dosage and Administration, Dosage Forms and Strength, Description, and How Supplied) and carton/container labeling, based on compliance with current Guidances and FDA policies were considered and incorporated into FDA proposed labeling were conveyed to Amgen in FDA-proposed labeling revisions.

4. Nonclinical Pharmacology/Toxicology

No new non-clinical pharmacology or toxicology data were submitted in the original supplement, however the CR letter issued October 24, 2008 contained information requests from the non-clinical reviewers requesting that Amgen provide the source of the data used to derive the multiples of human exposure from rat and rabbit reproductive toxicity studies cited in the product labeling. The resubmission contained 5 of 8 non-clinical study reports addressing reproductive toxicology data and the non-clinical reviewer determined that the information provided supported inclusion of the Amgen-proposed information in product labeling. The dosing in non-clinical studies was described in mcg/kg doses however extrapolation of animal PK data to human exposure was not included in product labeling due to uncertainty regarding the assay specificity used, variability of human PK, and inability to determine the impact of disease on human pharmacokinetics (animals were healthy). All non-clinical reviewer comments regarding the package insert were considered and incorporated into FDA proposed labeling to be appended to the CR letter.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology data were submitted in or required for review of this supplement. The clinical pharmacology reviewer proposed modifications to the existing label for conformance with the PLR format, to be conveyed to Amgen as an appendix to the CR letter. No new data were provided in the resubmission and minor changes recommended by the Clinical Pharmacology reviewer to conform with current Guidances and enhance clarity were incorporated into section 7 and 12.3 of the FDA's proposed product labeling.

6. Clinical Microbiology

No clinical microbiology data were submitted in or required for review of this supplement as determined by the CMC reviewer.

7. Clinical/Statistical-Efficacy

The proposed class labeling changes, submitted in response to items 3, 4, and 5 of FDA's May 31, 2007 letter, were supported by subject-level data from 23 individual studies, chosen because of study design characteristics, and on analyses conducted in pooled data within subgroups based on the source of ESA (darbepoetin alfa or epoetin alfa) The study design characteristics utilized in selecting datasets for inclusion in the pooled analysis were that data were available for individual study subjects participating in randomized, double-blind, placebo-controlled trials sponsored or supported by Amgen or J&JPRD or one of its affiliate companies. The studies included in the pooled analysis of each subgroup are listed below and identified by protocol number.

- Aranesp studies
  20010119, 980291 schedule 1, 980291 schedule 2, 990114, 980297, 20000161, 20010103, 20010145, 20020149, 20030204, 20030232

- Epoetin alfa studies
  [I88-036, I87-018/OEO-U24, I87-019/OEO-U25], [I88-037, I87-016/OEO-U22, I87-017/OEOU23], J89-040, CC2574-P-174, EPO-INT-1, EPO-INT-2, EPO-INT-3, EPO-INT-10, EPO-INT-76, N93-004, PR-27-008 (NCCTG 97-92-53), EPO-CAN-15

Key details of the study designs are presented in the following tables below.

Additional details regarding these studies were requested during the review; Amgen's responses have not addressed all of FDA's needs for additional information for 7 clinical studies, which will be needed if these studies are to be used to support labeling claims. Specifically, FDA will request individual study-specific data for all the studies used in combined analyses in the CR letter.

Amgen also provided the following information
- Revised package insert labeling in PLR format
- A rationale document discussing the approach to the re-analysis of safety information in the proposed package insert
- A rationale document discussing the specific data supporting proposed labeling (or lack of proposed labeling) in response to items 3, 4, and 5 of the May 31, 2007 letter
- Proposed modifications to for inclusion of updated information on two studies already included in the product labeling, the BEST study (Cancer Study 1) and the study conducted in anemic patients not receiving chemotherapy (Cancer Study 8)
- Proposed new language to include the results of Study 20010145
- Proposed language, contained in earlier versions of product labeling but removed during previous labeling revisions, to include the results of Study N93-004.

Study Identifier	Design	Total subjects (ESA : Placebo)	Population	Hemoglobin entry criteria	Treatment Duration	Product Schedule	Upper Hgb Limit Resulting in Dose Modification	Harmful Effects reported
980291 Schedule 1	Randomized placebo-control, dose-ranging, parallel group	249 (32:17:46:28:35: 40:51)	Anemic patients with solid tumors receiving multicycle chemotherapy	≤ 11 g.dL	12 wks (blinded phase)	darbepoetin alfa 4.5, 6.75, 9 , 12, 13.5, or 15 mcg Q3W	≥15 g/dl (men) ≥14 g/dL (women)	N
980201 Schedule 2	Randomized placebo-control, dose-ranging, parallel group	156 (31:31:33:30:31)	Anemic patients with solid tumors receiving multicycle chemotherapy	≤ 11 g.dL	12 wks (blinded phase)	darbepoetin alfa 9, 12, 15, or 18 mcg/kg Q4W	≥15 g/dl (men) ≥14 g/dL (women)	N
990114	Randomized (1:2:2:1) placebo-control, dose-ranging, parallel group	66 (11:22:22: 11)	Anemic patients with lymphoproliferative cancers receiving multicycle chemotherapy	≤ 11 g.dL	12 wks	darbepoetin alfa 1.0, 2.25, or 4.5 mcg/kg QW	≥15 g/dl (men) ≥14 g/dL (women)	N
980297	randomized (1:1) placebo-control	314 (156:158)	Anemic patients with lung cancer receiving multicycle platinum-based chemotherapy	≤ 11 g.dL	12 wks	darbepoetin alfa 2.25 mcg/kg QW	≥15 g/dl (men) ≥14 g/dL (women)	N
20000161	randomized placebo-control	344 (174:170)	Anemic patients with lymphoproliferative cancers receiving multicycle chemotherapy	≤ 11 g.dL	12 wks	darbepoetin alfa 300 mcg QW	≥15 g/dl (men) ≥14 g/dL (women)	N
20030232	randomized placebo-control	386 (193:193)	Anemic patients with non-myeloid cancers receiving multicycle chemotherapy	≤ 11 g.dL	15 weeks	darbepoetin alfa 300 mcg Q3W	Hgb ≥13 g/dL Hgb increase 1 g/dL in 14 days	No
20010145	randomized placebo-control	596 (298:298)	Patients with SCLC receiving multicycle platinum/etoposide chemotherapy	Hgb ≥ 9 g/dL and ≤ 13 g/dL	24 weeks	darbepoetin alfa 300 mcg QW x 4 →300 mcg Q3W	≥14 g/dL	No

Study Identifier	Design	Total subjects (ESA : Placebo)	Population	Hemoglobin entry criteria	Treatment Duration	Product Schedule	Upper Hgb Limit Resulting in Dose Modification	Harmful Effects reported
20010103	Randomized; stratified by baseline Hb (<10 vs. ≥ 10 g/dL) placebo-control	985 (515:470)	Anemic patients with non-myeloid cancers receiving no therapy; of hormonal or biologic therapy (i.e., non-myelosuppressive)	≤ 11 g.dL	16 weeks	darbepoetin alfa 6.75 mcg/kg Q4W	>12 g/dL	Yes
20020149	randomized placebo-control extension study of 20010103	371 (198:173)	Anemic patients with non-myeloid cancers receiving no therapy; of hormonal or biologic therapy (i.e., non-myelosuppressive)	Participation in 20010103	16 weeks	darbepoetin alfa 6.75 mcg/kg Q4W	>12 g/dL	Yes

FDA Reviewers' Assessment of the Amgen's Analysis Approach

Both the statistical and the clinical review staff raised concerns regarding the validity of Amgen's approach to the assessment of adverse effects of ESAs.

With regard to assessment of effects on overall survival, the review teams noted that there is potential bias based on the selection of studies included in this analysis, in that some studies specifically designed to assess effects on overall survival have not been included (e.g., DAHANCA10 study). Of those studies included, several were not well-designed to assess effects on survival, in that they did not control for confounding factors resulting from enrollment of a heterogeneous patient population with regard to underlying disease and cancer treatment. In addition, the studies were heterogeneous with respect to extent of follow-up for survival. As noted by Dr. Rothmann, there are methodological issues raised by the primary (Peto's odds ratio of death) and sensitivity (Mantel-Haenszel analysis for relative risk of death). Reproduced below are Dr. Rothmann's summarization of these methodologic issues (abstracted from his review):

- The *Peto's odds ratio of death* is based solely on the number of known deaths and total number of patients in each arm. Patient follow-up and survival times are not considered.

- The Peto's odds ratio of death within a study (or across studies) is not interpretable, since the intended follow-up is different among patients within the same study.

- For the meta-analysis of the Peto's odds ratio of death, the weight given an individual study does not increase as the number of events/the amount of follow-up increases (some studies are given less weight than studies having fewer events/having less follow-up). Within an individual study the standard error for the log of the sponsor's Peto's odds ratio of death is U-shaped. At the start of the study the standard error decreases as follow-up increases, reaches a minimum, and then increases as follow-up continues to increase. For further details see Section 3.1.2.1.

- The Mantel-Haenszel sensitivity analysis for the relative risk of death is likewise based solely on the number of known deaths and total number of patients in each arm. Patient follow-up and survival times are not considered. Likewise, it is not interpretable since the intended follow-up is different among patients within the same study. Also, within a study the relative risk of death will necessarily tend to 1 as follow-up increases. Thus, having 1 in a confidence interval for the relative risk of death from an individual study or meta-analysis of studies does not mean much.

- For the Mantel-Haenszel sensitivity analysis for the relative risk of death, the weight given a study's relative risk for the "meta-analysis"/integrated analysis is the harmonic mean of the number of patients in the two arms (this is typical and appropriate for binary outcomes). However, this does not take into account the number of deaths or i.e., how extensive the follow-up. Equal sized studies having the same randomization ratio (e.g., 1:1) are given the same weight regardless of any difference in the follow-up of overall survival. For a meta-analysis of the log-hazard ratio, a proper measure of the relative

difference in the two overall survival distributions, the study estimates are weighted by the harmonic mean of the number of events in each arm, not the harmonic mean of the number of patients in the two arms. Studies having poor follow-up (a small fraction of events) are overemphasized in the sponsor's integrated analysis of relative risk.

Dr. Fan and Dr. Shen both noted limitations in the interpretation of the pooled data based on differences across studies in underlying primary cancer type and stage, differences in chemotherapy regimen, and differential length of follow-up. For these reasons, analysis of results by study rather than by pooling results may be more valid where distinctions in study population and length of followup can be appropriately weighted. Additional limitationa, both for individual studies and for the pooled analysis, are the lack of prospective stratification at randomization for baseline hemoglobin levels and the lack of prospective designs assessing appropriate duration of treatment or maximum hemoglobin targets.

FDA Reviewers' assessment of Amgen's proposed labeling changes

Item 3 from the May 31, 2007 letter

> Revision of the INDICATIONS AND USAGE section to clarify the severity of anemia for which Aranesp/PROCRIT is indicated, by inclusion of the maximum, and if appropriate minimum, pretreatment hemoglobin level.

Amgen proposed addition of the following text to Dosage and Administration section of the label:

(b) (4)

(b) (4)

FDA Review of Amgen's proposal

Since the initial submission in December 2007, the product label has been modified as described in Section 2 of this summary review. The following safety labeling change ordered under 505(o) was approved on August 5, 2008 and included the statement

"*Do not initiate Epogen/Procrit for hemoglobin >10 g/dL*"

Based on this action, Amgen's proposed labeling language was replaced with the safety-ordered language.

I concur with the assessment of the clinical and statistical reviewers that Amgen did not provide adequate justification for the proposed target of (b) (4) in their original presentation and that these data did not result in a determination that the proposed target was better

supported that the language ordered for inclusion in product labeling by FDA. The FDA reviewers assessment of the rationale provided by Amgen in support of their initial proposal [redacted] (b) (4) is summarized below.

As noted by Dr. Fan, there was no evidence, based on the results of Study 20010103, that anemic cancer patients who are not receiving concomitant myelosuppressive chemotherapy benefit from treatment with Aranesp.

Dr. Fan also noted that all randomized studies in which Aranesp was administered to patients receiving concurrent chemotherapy demonstrated a significantly lower rate of RBC transfusions, both for the individual study results overall and in the pooled analysis. In addition, exploratory analyses in hemoglobin subsets from the pooled dataset, as presented by Amgen, or within individual studies, are presented in the reviews by Drs. Fan and Shen of the FDA, showed evidence of a reduction in transfusion requirements for Aranesp-treated patients regardless of the selected baseline hemoglobin level. The magnitude of the treatment effect (absolute reduction in risk of approximately 20%) was similar within subgroups defined by baseline hemoglobin, however the risk of being transfused was inversely related to the baseline hemoglobin (greatest risk in those with the lowest hemoglobin levels). Both Dr. Fan and Shen concluded that the results of analyses within *post-hoc* exploratory subgroups were suspect because of the lack of stratification for baseline hemoglobin. The same concerns regarding the validity of comparisons in post-hoc exploratory subgroup analyses by baseline hemoglobin for safety parameters (OS and VTE). Dr. Fan stated that these data were not adequate to support any specific level of hemoglobin at which Aranesp should be initiated; she further noted that individual judgment based on patient factors and planned treatment should be considered.

For these reasons, and considering the advice of the March 2008 ODAC, FDA ordered safety language stating that initiation of an ESA should occur only when the hemoglobin was less than 10 g/dL in order to make the drug available to patients with the highest apparent need for RBC transfusions, based on highest proportion of patients at risk for transfusion and noting that the absolute reduction in risk of transfusion appears grossly similar in the various subgroups.

Item 4 from the May 31, 2007 letter

> *Revision of the DOSAGE AND ADMINISTRATION section to specify a lower maximum hemoglobin level (ie, hemoglobin level less than 12 g/dL) at which dosing should be suspended or terminated.*

In the original supplement, Amgen proposed no changes to the Dosage and Administration section of the product label approved as of Nov. 8, 2007, reproduced below.

Amgen stated that the existing data strongly support the appropriateness of the current hemoglobin upper limit of 12 g/dL. Amgen and J&JPRD therefore propose that the current label guidance to withhold ESA administration if hemoglobin levels exceed 12 g/dL should be retained, in accordance with the recommendations of the May 10, 2007 ODAC and other major health authorities. Amgen supported their determination that no changes were needed by citing recent labeling changes approved November 8, 2007 (STN BL 10395164/) that identified a hemoglobin level of 12 g/dL the upper safety limit for dosing and the inclusion of the following in the Boxed Warning section of the label:

- ESAs shortened overall survival and/or time-to-tumor progression in clinical studies in patients with advanced breast, head and neck, lymphoid, and non-small cell lung malignancies when dosed to target a hemoglobin of ≥ 12 g/dL.
- The risks of shortened survival and tumor progression have not been excluded when ESAs are dosed to target a hemoglobin of < 12 g/dL.

In addition, Amgen submitted results of a Cochrane meta-analysis that presented the odds ratios for overall survival from the published literature. The analysis was limited to randomized, controlled trials in which the ESAs were initiated only in patients with a hemoglobin of less than 12 g/dL and results were grouped by the threshold limit for discontinuation of the ESA (i.e., 13, 14, 15, or 16 g/dL). In this analysis, the odds ratio for survival was less than 1.0 in all but one group, however in all groups, the upper limit for the 95% confidence interval for the reported odds ratio was always greater than 1.0, thus the potential for harmful effects could not be excluded.

Amgen also presented analyses of the pooled dataset of all placebo-controlled, randomized, company-sponsored or supported trials. These analyses were displayed as Forest plots in which the outcomes of patients for patients after reaching a hemoglobin of 12 g/dL or higher (termed "responders") were compared to the outcomes in patients who did not or had not yet achieve a hemoglobin of 12 g/dL.

The outcomes evaluated in the pooled analyses of darbepoetin alfa were: on-study death, death on follow-up, disease progression on study and with follow-up, progression-free survival (PFS) on-study and with follow-up, cardiovascular/thromboembolic events, and thrombosis/embolism. The outcomes were better for "responders", i.e., patients with hemoglobin levels of greater than 12 g/dL than for those with hemoglobin levels of ≤ 12 g/dL

within treatment arms (i.e., the hazard ratio was less than 1.0, indicating better results among patients with higher hemoglobin both for those who were treated with darbepoetin alfa and for those who received placebo as compared to patients with lower hemoglobin levels regardless of treatment) for all but one comparison (thrombosis/embolism) where outcomes favored patients receiving darbepoetin alfa who also failed to achieve a hemoglobin of 12 g/dL.

FDA Review of Amgen's proposal

Since the initial submission in December 2007, the product label was modified as described in Section 2 of this summary review. The final labeling approved on August 5, 2008 contained the following information in the Dosage and Administration subsection for Cancer Patients on Chemotherapy:

(b) (4)

(b) (4)

FDA's assessment of Amgen's rationale for retaining language from Nov. 2007 is summarized below.

The statistical and clinical reviewers rejected Amgen's proposal not to modify the Dosage and Administration section for Cancer Patients on Chemotherapy for different reasons. The statistical reviewer and statistical team leader rejected Amgen's proposal because they rejected the validity of the analyses presented to show that patients with a hemoglobin of greater than 12 g/dL are not harmed. Specifically, the statistical team questioned the validity of the meta-analysis based on use of odds ratios (for the reasons discussed extensively at the beginning of section 7 of this review). They also raised concerns regarding the appropriateness of pooling results from studies that enrolled different patient populations, receiving different background therapy, and dosing regiments for the ESA which differed not only in dose and schedule but in dosing directions (e.g., different recommendations for dose modification).

The clinical reviewer noted that statisticians' assessment of the analyses and agreed that the data did not support the proposed "target". However, she also stated that there is no evidence which directly addresses this question and recommended that the target be left to the treating physician's discretion.

I concur with the conclusions of the statisticians and Dr. Fan that the data provided by Amgen do not support the safety of the hemoglobin target of 12 g/dL as the maximum threshold which should result in withholding of darbepoetin alfa. I do not concur with Dr. Fan's statement that product labeling should remain silent on this issue or leave it to the discretion of physicians. Studies conducted in patients with cancer and in patients with chronic renal failure have indicated that outcomes are poorer with a higher hemoglobin threshold and in the absence of data, I find it prudent to accept the advice of the ODAC and others to target a threshold where transfusions would be avoided. This threshold should be below 12 g/dL and, if consistent with transfusion guidelines, would be closer to 8-9 g/dL. In the absence of clear data from adequately designed and conducted studies, the threshold included in product labeling on Nov. 2007 (10 g/dL) is with a range that would generally not require transfusions. Therefore, I agree with the retention of the labeling accepted in Nov. 2007.

In addition, I agree with the comments made by Amgen regarding their analyses, i.e., that the presence of higher hemoglobin is associated with better outcomes, this does not treatment to achieving that higher hemoglobin results in these better outcomes; this is particularly notable since better outcomes are also present in the placebo-treated arms. The entire approach is to compare make comparisons based on patient responsiveness to the drug, which is likely to be confounded by many patient factors, rather than the impact of a treatment strategy designed to achieve a specific hemoglobin target. In fact, these are the very studies in which signals emerged and there are no data to establish a lower hemoglobin target. Therefore, Amgen should complete the studies required as post-marketing commitments to establish the safety of the recommended dose and schedule in accordance with current labeling.

Item 5 from the May 31, 2007 letter

> Revision of the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections to indicate that Epogen/Procrit should be discontinued following the completion of the concomitant chemotherapy regimen.

Amgen proposed the following additions to product labeling

Boxed Warnings section:

FDA Review of Amgen's proposal

Since the initial submission in December 2007, the product label has been modified as described in Section 2 of this summary review. The approval of a safety labeling change ordered under 505(o) was approved on August 5, 2008 to include the following statements

Boxed Warning

> *"Discontinue following the completion of a chemotherapy course."*

Dosage and Administration: Cancer Patients on Chemotherapy

> *"Discontinue EPOGEN/PROCRT following the completion of a chemotherapy course"*

Based on this action, FDA replaced Amgen's proposed language with the safety ordered language.

(b) (4)

Dr. Fan also noted that, in light of the poorer survival outcomes in study 20010103 where patients received Aranesp but no chemotherapy, the available evidence suggests that continued dosing is unsafe and futile (there was no evidence of a reduction in transfusions). For this reason, Dr. Fan recommended that labeling require discontinuation of Aranesp dosing with the last chemotherapy dose.

In the resubmission, Amgen provided datasets and analysis programs supported the proposed data to be included in section 14.2 regarding demographic and transfusions rates for studies C1 and C2 (Protocols 980297 and 20030231). Drs. Shastri and Shen proposed minor editorial changes to Section 14.2 which were conveyed to Amgen.

I concur with Drs. Shastri's and Shen's conclusions and agree with their proposed modifications to Amgen's labeling.

8. Safety

This application was provided in response to FDA requests for revision to product labeling to enhance safety. The rationale for Amgen's proposed labeling rests on aggregate analysis of efficacy (transfusion requirements) and safety [risk of vascular thrombotic events (VTE) and risk of death] from 23 randomized, placebo-controlled trials conducted by or supported by Amgen or Ortho Biotech. In addition, Amgen provided a meta-analysis of published literature assessing the risks of death and of VTE. None of these data used in this analyses were new and no new safety signals were provided.

In addition, the application contained safety data to permit a re-assessment of safety information presented in the Adverse Reactions section of product labeling, conducted in support of conversion of the product label to PLR format. The safety datasets contained data from studies previously reviewed by FDA in support of approved labeling claims.

No new safety signals were identified through this re-analysis of the data, however the Adverse Reactions section was updated to reflect only those events occurring more frequently in the darbepoetin alfa-treated patients. Details of the FDA's approach to analysis of safety data and basis for inclusion in the Adverse Reactions sections of product labeling are described in the clinical reviews for this supplement.

Amgen also proposed updates to the Warnings and Precautions section of the labeling, describing the results of an "updated" analysis for Study 20010103 (Cancer Study 8) under the "Increased Mortality and/or Tumor Progression section (5.2)" of the product labeling. Data currently in the product labeling were obtained using the analysis data cutoff date of November 7, 2006, whereas the additional data include results through the data cut-off date of March 23, 2007. Amgen noted that this was a *post-hoc* analysis, stating that "The hazard ratio of time to all deaths for the darbepoetin alfa and placebo groups, based on the Cox regression analysis stratified by the factors used at randomization but unadjusted for covariates, was (b) (4) However, the hazard ratios and statistical significance diminished when post-hoc analyses were further adjusted for baseline imbalances or known prognostic factors." Based on this post-hoc analysis, Amgen proposed the following modification to product labeling (in bold)

> *"Cancer Study 8 was a Phase 3, double-blind, randomized (Aranesp vs. placebo), 16-week study in 989 anemic patients with active malignant disease, neither receiving nor planning to receive chemotherapy or radiation therapy. There was no evidence of a statistically significant reduction in proportion of patients receiving RBC transfusions.*
>
> (b) (4)

Amgen also proposed to modify language in sections 5.1 and 5.2 of the Warnings and Precautions section of the product labeling to describe "updated" results of the BEST study (Cancer Study 1). The BEST study was terminated prematurely awhen interim results demonstrated that higher mortality at 4 months (8.7% vs. 3.4%) and a higher rate of fatal thrombotic events (1.1% vs. 0.2%) in the first 4 months of the study were observed among subjects treated with epoetin alfa. At the time of study termination, the Kaplan-Meier estimated 12-month survival was also lower in the epoetin alfa group than in the placebo group (70% versus 76%; hazard ratio 1.37, 95% CI: 1.07, 1.75; p = 0.012). Amgen now proposes to add the "updated" information from long term-follow-up of the BEST study as follows:

> (b) (4)

I concur with the conclusions of Dr. Fan and Dr. Shen that these are exploratory *post-hoc* analyses that do not contribute important new safety information. With regard to the BEST trial, FDA review staff concluded that the definitive analysis is that which resulted in termination of the trial. Beyond that

timepoint, the trial design was substantially altered by discontinuing ESA treatment. Amgen again proposed inclusion of "updated" results in the product labeling in the resubmission. Drs. Shastri and Shen reached the same conclusion as in the original review and proposed that the results as in current product labeling be retained.

I concur with the conclusions of the reviewers for this application and of BL STN 103234/5166 that these are exploratory *post-hoc* analyses that do not contribute important new safety information. With regard to the BEST trial, FDA review staff concluded that the definitive analysis is that which resulted in termination of the trial. Beyond that timepoint, the trial design was substantially altered by discontinuing ESA treatment.

In the resubmission:

- Amgen's proposed labeling included the term "adverse event" in Adverse Reactions section of the physician product labeling. Dr. Shastri recommended that this term be replaced with the term "adverse reactions" as per FDA Guidances and based on the selection of inclusion of terms in this section. Adverse reactions for cancer studies are denoted for those reactions identified as occurring at higher incidence in placeb0-controlled trials. Adverse reactions for studies in patients with chronic renal failure were active controlled (vs. epoetin alfa); rates are provided for adverse reactions identified in placebo-controlled studies of epoetin alfa or with high biologic plausibility based on the product class.

- Amgen's proposed labeling included data describing the incidence of thromboembolic adverse reactions across a pooled dataset containing the results of seven randomized, controlled trials (Protocols 990114, 980291- schedules 1 and 2, 908297, 20000161, 20010145, and 20030232). Drs. Shastri and Shen confirmed Amgen's results and included the data in a table designated for such events. Drs. Shastri and Shen also confirmed the accuracy of the text describing the pooled dataset.
- [redacted] (b) (4) that there are sufficient data from controlled clinical trials submitted to the supplement to adequately describe these risks.

- Amgen proposed to modify the results of Study 3 (the PREPARE study) in the Warnings and Precautions section by describing the results as "interim". Drs. Shastri and Shen stated that this qualifier was not appropriate as the results reflect data which resulted in early termination of the protocol and thus represent the final study results. This was conveyed to Amgen in the FDA-proposed labeling revisions.

- Amgen proposed to modify the results describing Study 6 (the DAHANCA study) in the Warnings and Precautions section by describing the results as derived from an [redacted] (b) (4) analysis. Drs. Shastri and Shen stated that this qualifier was not accurate as the number of events at the time of this analysis (158) closely approximated the number of events in the statistical analysis plan for the planned interim analysis (150). Therefore, the reviewers indicated that "formal interim analysis" would be a more accurate description.

All clinical and statistical reviewer comments (see reviews by Drs. Chaohong Fan, Minh-Ha Tranh, Kaushik Shastri, and Yuan-Li Shen) regarding the package insert were considered and incorporated into FDA proposed labeling to be appended to the CR letter.

9. Advisory Committee Meeting

There were three meetings of the Oncologic Drugs Advisory Committee (ODAC) in which FDA to seek advice regarding the safety of Erythropoiesis-stimulating agents (ESA) for treatment of anemia due to cancer chemotherapy. The first ODAC was held in May 2004 and the second was held in May 2007, both of which were prior to submission of this supplement. However, a third ODAC meeting was held on March 13, 2008 based on the results of additional studies, not presented at the May 2007 ODAC, which suggested or demonstrated harmful effects. The March 13, 2008 ODAC meeting was convened to review the results of two additional trials (GOG-191 and PREPARE) and progress made on addressing the risks of ESAs since the 2007 ODAC, in order to provide advice on Amgen's and FDA's proposed risk mitigation strategies. The key issues on which ODAC advice was sought was whether available data continue to demonstrate that there is a favorable benefit to risk relationship for ESA use for treatment of chemotherapy-induced anemia in patients with cancer and if so, whether the current product labeling is sufficient to ensure safe and effective use.

The following questions, posed to the ODAC, and the Committee's response are summarized:

1. Considering all the available data on the benefit and risks of ESAs in the treatment of anemia due to concomitant cancer chemotherapy, do you recommend that these products continue to be marketed for the indications listed above?

   - *Panel members noted that ESAs are more convenient than blood transfusions with one panel member questioning whether there was hard data on the benefit of ESAs other than convenience.*
   - *A point was noted that there may not be a quality of life benefit*
   - *It was questioned that based on the data, ESAs could be 2nd line therapy with possible use in patients whom transfusion was not appropriate.*
   - *Overall, the committee agreed that these products should continue to be marketed for the indication listed in Question 1.*

   Vote : ***Yes=13*** ***No = 1*** ***Abstain = 0***

2. If you recommend that the current indication should be retained, should FDA require that product labeling be modified? Below are four potential approaches to mitigating risks through revised labeling. Please address each of them separately.

   a. **Vote**: To date, only clinical trials in small cell lung cancer have reasonably excluded an increased risk for death among patients receiving ESAs. Trials have demonstrated an increased risk of death and/or tumor promotion in head/neck, non-small cell lung cancer, breast (neoadjuvant and metastatic settings), lymphoid malignancies, and cervical cancers. Tumor types, other than those listed above, have not been adequately studied. ***Should the current indication be modified to restrict use only to patients with small cell lung cancer?***

   - *One panel member noted that ESAs should only be approved in disease where there is little/no risk while other settings require additional studies.*

   Vote : ***Yes=6*** ***No = 8*** ***Abstain = 0***

   b. **Vote**: The PREPARE trial demonstrated decreased relapse-free and overall survival in breast cancer patients receiving neoadjuvant chemotherapy. The risk/benefit assessment is different for patients receiving neoadjuvant and adjuvant chemotherapies than for patients with metastatic or incurable cancers. ***Should the current indication be modified to include a statement that ESA use is not indicated for patients receiving potentially curative treatments?***

   - *One panel member noted that those with metastatic disease should not receive ESAs any different than those in the adjuvant setting.*
   - *One panel member noted that using ESAs in the curative group, may convert from a curative patient to a non-curative patient.*

- *Overall, the panel agreed that the current indication should be modified to include a statement that ESA use is not indicated for patients receiving potentially curative treatments.*

Vote : ***Yes=11*** ***No = 2*** ***Abstain = 1***

c. **Vote**: Although increased tumor promotion and/or decreased survival have been demonstrated in several tumor types, adverse findings have been duplicated in two malignancies—breast cancer and head and neck cancer. ***Should the current indication be modified to include a statement that ESA use is not indicated for patients with breast and/or head & neck cancers?*** (If yes, please specify breast and/or head & neck cancer).

- *Panel members questioned the definition/appropriateness of the terminology "tumor progression" and "tumor promotion" in regards to the use of ESAs.*
- *It was noted that the question could also read with "metastatic" in front of breast and/or head &neck cancers.*

Vote : ***Yes=9*** ***No = 5*** ***Abstain = 0***

d. The only objective evidence of efficacy demonstrated for ESAs has been avoidance of RBC transfusions; however, not all patients with anemia require an RBC transfusion. Product labeling does not specify the hemoglobin level at which ESA treatment should be initiated. ***Assuming a patient is asymptomatic and has no co-morbid conditions, please specify the hemoglobin level at which initiation of an ESA is appropriate.***

- *Panel members agreed that treatment should be based on physician judgment and tailored to individual patients. Panelists did not feel that setting levels was appropriate for a hypothetical patient.*

3. If the Committee recommends that the indication for treatment of anemia due to concomitant chemotherapy should be retained (as currently approved or with additional labeling changes as above), discuss additional strategies that FDA could require to minimize risk. Below are two options that could be considered. If you have other suggestions, please state them.

a. **Vote**: An informed consent/patient agreement would explicitly require the oncology patient's authorization or agreement to undergo treatment with an ESA. Both patient and physician (or designate) signatures would be required. In the process, the physician prescribing the ESA treatment would discuss the risks and benefits of ESA therapy and alternative treatments. ***Should the FDA require the implementation of an informed consent/patient agreement for the treatment of chemotherapy induced anemia?***

(Question 3a-b was clarified to ask for the principle instead of the logistics of the informed content/patient agreement)

- ***The panel agreed that adequate patient education is necessary, however disagreed on whether a written informed consent should be required***

Vote : ***Yes=8*** ***No = 5*** ***Abstain = 1***

b. **Vote**: Examples of restricted distribution programs include STEPS (thalidomide), RevAssist (lenalidomide), and iPLEDGE (isotretinoin). Restricted distribution systems link product access to planned safe and effective use. These programs may require identification and enrollment of healthcare providers who agree to prescribe only in accordance with product labeling and who commit to patient education regarding safe use. Registration of patients may also be required. Certain patient characteristics would be recorded at individual patient registrations (e.g., hemoglobin, chemotherapy type, malignant diagnosis). ***Should FDA mandate a restricted distribution system for oncology patients receiving ESAs?*** *YES or NO*

Vote : ***Yes=1*** ***No = 10*** ***Abstain = 2***

- *The committee agreed that a restricted distribution system was not necessary in regard to the above question. It was noted that to address the issue of safety, physician incentives should be reduced.*

10. Pediatrics

Not applicable to this application as a new indication, new dosing regimen, or new presentation was not sought.

11. Other Relevant Regulatory Issues

Division of Scientific Investigations audits were not requested for any studies since most of the studies included for the combined analysis were more than 10 to 15 years old and primary records would not be available.

12. Labeling

No changes to the proprietary name or carton/container labeling were proposed by Amgen and the FDA did not identify need for modifications to these components of product labeling in the original submission. Verbal comments provided by DDMAC and OSE during labeling meetings were considered and incorporated as appropriate in FDA proposals for revisions to the submitted product labeling.

Amgen has requested changes to product labeling in response to FDA's request for a labeling supplement, as discussed in Section 7 of this review. In the original submission (Dec. 26, 2007), Amgen proposed additional labeling changes not requested by FDA

- An update to clinical information on Study 20010103 (Cancer Study 8) in the WARNINGS AND PRECAUTIONS, Increased Mortality and/or Tumor Progression section (5.2) of the label. The updated information is derived from survival data obtained in a post-treatment follow-up period. The current labeling section is reproduced below with the change in bold font:

  "Cancer Study 8 was a Phase 3, double-blind, randomized (Aranesp vs. placebo), 16-week study in 989 anemic patients with active malignant disease, neither receiving nor planning to receive chemotherapy or radiation therapy. There was no evidence of a statistically significant reduction in proportion of patients receiving RBC transfusions (b) (4)

  FDA Assessment: The clinical and statistical reviewer have rejected this proposed change because the trial was terminated based on the earlier analysis, which is therefore the most relevant information for inclusion in Warnings and Precautions section of the labeling. Additional analyses with updated information are considered by FDA as exploratory only and should not be included in the label

- (b) (4)

  FDA Assessment: Both the clinical and statistical reviewer rejected inclusion of this study in the Warnings and Precautions section. This study did not show an increase in mortality and therefore does not specifically address the risks described in this section. Inclusion of these trial results may serve to mitigate the Warnings and therefore was determined to be inappropriate by the clinical reviewer. Details of the analysis of this study were conducted under STN BL 103951/5175

- An update of clinical information on the "BEST" Study (Cancer Study 1) in the WARNINGS AND PRECAUTIONS section of the label. The proposed new language to be included in the label is reproduced below

(b) (4)

FDA assessment: The clinical and statistical reviewers have rejected this proposed modification to language in the current labeling. The reviewers find this "updated" data not acceptable for inclusion in the labeling because the trial was terminated based on the earlier analysis, which is therefore the most relevant information for inclusion in Warnings and Precautions section of the labeling. Additional analyses with updated information are considered by FDA as exploratory only and should not be included in the label

- (b) (4)

FDA Assessment: Both the clinical and statistical reviewer rejected inclusion of this study in the Warnings and Precautions section. This trial did not demonstrate an increase in mortality and therefore does not specifically address the risks described in this section. Inclusion of these trial results may serve to mitigate the Warnings and therefore was determined to be inappropriate by the clinical reviewer. Further, the reviewers note that the intent of the trial was to demonstrate non-inferiority of objective response rates, was stopped early (after 224 of 400 planned patients) and thus is able to rule out impairment of survival due to early termination and lack of a pre-specified hypothesis in the trial for this outcome.

FDA reviewers recommended numerous additional modifications to Amgen's proposed package insert. The changes are briefly itemized below.

(1) Boxed Warning

a. "minimize" changed to "decrease" because of the lack of certainty regarding the magnitude of the reduction in the risk in patients who receive any amount of an ESA.

b. (b) (4)

c. "adverse reactions" substituted for "adverse events" throughout labeling.

d. Inclusion of wording to reference the REMS program.

e. Information in the Boxed Warning presented in bullet form to enhance legibility.

(2) Indications and Usage section

a. New subsection "Limitations of Use" created to limit repetition of the same information across both indications.

b. Currently approved indications statements re-worded for brevity and clarity

c. Titles of subsections shortened for brevity.

d. Inclusion of wording to reference the REMS program.

(3) Dosage and Administration

a. Extensively revised for brevity and re-worded for "active voice"

b. References to "lack or loss of response" deleted; product labeling is not intended to cover aspects of general medical management (e.g., differential diagnosis of anemia) and clinical indications clarify the types of anemia for which Epogen is indicated.

(4) Dosage Forms and Strengths

Information in this section moved to section 16; remaining information shortened for brevity and consistency with other labeling.

(5) Warnings and Precautions

a. (b) (4)

b.

c. Section 5.2: Editorial changes to remove the word "Cancer" from the study titles as this may lead to confusion with references to studies in section 14.3. Also,

(b) (4)

d. Revised text describing results of study 6 for accuracy. The goals of treatment in the Aranesp arm were to achieve and maintain hemoglobin levels at levels above that which would be classified as anemia.

e. (b) (4)

f. Section 5.3 (Hypertension) revised to delete unnecessary information on (b) (4)

g. Moved up "Seizures" to section 5.4 as next most common serious adverse event. Revised for brevity and active voice

h. Deleted sections on "loss of response", "general", and "CRF patients not on dialysis". Product labeling should not include information related to general practice of medicine (i.e., differential diagnosis and diagnostic work-up of anemia) or to general care for underlying medical conditions.

i. Revised subsection on PRCA to remove references to deleted subsection on loss of response; edited for brevity and active voice.

j. Deleted subsection on Hematology. Relevant information now included in section on laboratory testing.

k. Subsection on Dialysis Management edited for brevity and critical information.

l. Subsection on Laboratory testing re-titled to clarify the focus of this subsection. Edited for brevity and active voice and to limit redundancy with D&A section.

m. (b) (4)

n. Addition of new subsection (5.2) to reference the approved REMS

(6) Adverse Reactions

a. Extensively edited for brevity and for consistency with current FDA Guidance on Adverse Reactions section of product labeling.

b. Adverse events probably unrelated to ESA's in the judgment of the Div of Hematology reviewer were removed from adverse event tables.

c. (b) (4)

d. The subsection on annualized rates of thrombotic events in patients with CRF deleted due to lack of confidence in ascertainment and completeness of follow-up, leading to a potential underestimation of the event rate.

e. Added subsection on Post-marketing Experience, with recommended caveats regarding inadequate information to characterized incidence of such reactions.

f. Immunogenicity subsection edited to delete phrase "other products in this class" for consistency with current Guidances on product labeling.

g. Amgen's proposal to use the term "adverse event" in this section, per the Oct. 26, 2009 resubmission, was deleted and replaced with the term "adverse reactions" as per FDA Guidances. Adverse reactions for cancer studies are denoted for those reactions identified as occurring at higher incidence in placeb0-controlled trials. Adverse reactions for studies in patients with chronic renal failure were active

controlled (vs. epoetin alfa); rates are provided for adverse reactions identified in placebo-controlled studies of epoetin alfa or with high biologic plausibility based on the product class.

h. Data describing the incidence of thromboembolic adverse reactions across 7 randomized, controlled trials were confirmed and included in a table designated for such events.; text description of the pooled dataset was determined to the acceptable.

i. [redacted] (b) (4) there are sufficient data from controlled clinical trials submitted to the supplement to adequately describe these risks.

(9) Use in Specific Populations

a. Pregnancy Category C: Editorial changes.
b. Nursing mothers: Animal data in this section moved to Non-clinical toxicology section. This section modified in accordance with recommendations from Maternal-Fetal Health team.
c. Pediatric Use: Re-worded for clarity. References to Clinical Pharmacology (12.3) and Clinical Studies (14.1) added. The term "conversion" replaced with "transition".
d. Geriatric Use: Minor editorial changes for clarity.

(10) Overdosage

- This section was revised to clarify both subacute and chronic effects of overdosage and to provide more specific directions regarding appropriate actions to be taken (e.g., drug discontinuation). Edited for brevity with deletion of non-essential information (e.g., information in Dosage and Administration on monitoring hemoglobin rate of rise).

(11) Description

- Edited for brevity and essential information; resulting in deletion of phrase "closely related to erythropoietin" and "additional carbohydrate chains increase the" as non-essential information.

(12) Clinical Pharmacology

a. Section on Mechanism of action: The majority of this section was deleted because it refers to endogenous erythopoetin rather than Aranesp or is either covered in other sections (PD or PK subsections of clinical pharmacology or Dosage and Administration section).
b. Section on PD: Replaced "until" with "for" in describing time to PD effect.
c. Section on PK: Editorial changes to spell out acronyms. Deletion of information on 2.25 mcg/kg dose from paragraph describing PK of Aranesp in patients with cancer as this is not an approved dose for an every-three-week schedule.

(13) Non-Clinical Toxicology

a. Section on Reproductive and Developmental Toxicology added and includes data previously described under Pregnancy subsection; the non-clinical data were moved to this section as recommended by the OSE consultant staff as the more appropriate section for these data.
b. Deleted information on tissue cross-reactivity in animal species and lack of proliferative effects in non-hematologic tissues, as findings are expected.

(14) Clinical Studies

a. In general, section revised for brevity and clarity and to include appropriate clinical trial description in accordance with the Guidance for Industry document on this section of the label.
b. Study results for N5 trial in pediatric patients with CRF added to this subsection.
c. General section describing design of studies supporting safety and efficacy in patients with cancer added. Subsequent paragraphs on the individual studies edited to delete information in introductory paragraph and for brevity and clarity. Description of the primary efficacy measures included. In Study C2 results, efficacy re-calculated based on primary efficacy population (for consistency with Study C1 and Epogen/Procrit analyses) of patients remaining on study between day 29 and end-of-treatment.
d. Data limited to primary efficacy endpoints and data used by FDA as primary support to expand labeling claims.
e. Inclusion of demographic information and crude transfusion rates for Protocols 980297 and 20030231 were deemed acceptable based on FDA's confirmation of the results through datasets provided in the resubmission.

(15) How Supplied and Handling Information

- Information previously provided in dosage forms and strengths moved to this section.

(16) Patient Counseling Information

- Re-placed previous patient labeling with Medication Guide; further labeling modification to be addressed under pending REMS supplement (BL STN 103951/5195).

Medication Guide

- Revised to refer to the REMS Program
- Updated common side effects of Aranesp for consistency with changes to the Adverse Reactions section of the Physician Package Insert

Patient Instructions for Use

- Minor editorial changes as recommended in by DRISK during labeling meetings

LABELING REVISIONS and REMS MODIFICATIONS BASED ON CLASS 1 RESUBMISSION (10395/5173) and REMS ASSESSMENT (103951/ 5258)

Physician Product Labeling

- **Boxed Warning**
  - Removed qualifier [redacted (b) (4)]" and added reference to Table 2 to first bullet under Cancer; the former to remove language suggesting uncertainty of effect and the latter to direct user to relevant data.
  - Revised first bullet under Chronic Renal Failure and 4th bullet under Cancer for brevity
- **Indications and Usage**
  - Added term "myelosuppressive" to cancer indication for accuracy and modified language "upon initiation, there is that will be two additional months of planned chemotherapy" for clarity and to reflect population in whom benefit has been shown.
  - Under Limitations of Use, the bullets under Aranesp is not indicated for use (b) (4) [redacted] were replaced with Aranesp is not indicated for use "In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure. " and "Aranesp has not been shown to improve quality of life, fatigue, or patient well-being."
- **Dosage and Administration**
  - The term "approximately" was removed throughout this section as it is vague and does not add value in providing directions for use
  - Minor editorial changes, including adding "Recommended" to title describing starting doses for the approved indications.
  - Added the phrase "and if there is a minimum of two additional months of planned chemotherapy" to the information under Recommended Starting Dose (2.3) to reflect the indicated population.
  - Modified section 2.4 to refer to specific presentation (vial, prefilled syringe) as appropriate and added the information "Do not use Aranesp that has been shaken or frozen." to this section.
- **Dosage Forms and Strengths**
  - Deleted references to the AutoClick Injector in this and all other applicable sections of product labeling (e.g., How Supplied, Patient Instructions for Use) based on Amgen's decision to discontinue this presentation.
  - Minor editorial changes for brevity
- **Warnings and Precautions**
  - Removed proposed language under Section 5.1, the subsection titled "Surgery Patients" as this information does not provide signficant information to inform users regarding patient risks.
  - Subsection 5.2: title modified to add name of drug, text modified to provide "command language" and for consistency with directions in REMS.
  - Title of Subsection 5.3 modified for accuracy

- Removal of subsection on "Albumin" as this is no longer in marketed formulation
- Removal of subsection on "Dialysis Management" as this information is described under Dosage and Administration.

- **Adverse Reactions**
  - Modified data in Table 4 on incidence of cerebrovascular disorders for both 20010145 and the pooled analysis.
- **Use in Specific Populations**
  - Deleted proposed language (b) (4) in section 8.1 as this information is provided in Seciton 13.
- **Overdosage**
  - Replaced proposed labeling (b) (4) with "Aranesp overdosage can cause hemoglobin levels above the desired level, which should be managed with discontinuation or reduction of Aranesp dosage and/or with phlebotomy, as clinically indicated *[see Pharmacodynamics (12.2)]*." This change more closely aligns with the Dosage and Administration section and the existence of a subset of patients who are hyporesponders.
- **Description & How Supplied**
  - Deleted references to polysorbate-containing and albumin-containing formulations and to the Sure-Click Autoinjector presentation.
- **Nonclinical Toxicology**
  - Replaced (b) (4) with "This animal dose level of 20 mcg/kg/day is approximately 20-fold higher than the clinical recommended starting dose, depending on the patient's treatment indication." as a more accurate description of this information.
- **Clinical Studies**
  - Added new section to describe the efficacy results of Protocol 20010145 (Study C3) in section 14.2, to provide context for the safety data that are provided in the Adverse Reactions section under the subsection on Patients with Cancer.
- At end of prescribing information, the following text has been added "This product's label may have been revised after this insert was used in production. For further product information and the current package insert, please visit www.amgen.com or call our medical information department toll-free at 1-800-77AMGEN (1-800-772-6436)."

Medication Guide

- Instructions regarding when to read the Medication Guide modified for consistency with current REMS and FDA's enforcement discretion letter
- Additional changes for sixth-grade level languate
- Changes to confirm with revised Indications and Usage section in Physician Package insert
- Subsections created under "How Should I Take Aranesp" which contain information specific to patients with cancer and information relevant for all patients

- Section on common side effects of Aranesp revised to remove (b) (4) as this is discussed in greater detail in the section immediately preceding on serious side effects of Aranesp
- Information on presentations and formulations that are no longer marketed removed.

REMS template, supporting document, and website materials

- The REMS template was extensively revised on the recommendation of the DRISK review staff for consistency with FDA's current policy on the content of this document; in general, certain items were removed from the template that are also contained in the supporting document.
- Modification to permit specified allowable modifications to the APPRISE Oncology Program Patient and Healthcare Professional (HCP) Acknowledgment Form and to allow electronic archival of the document as part of an electronic medical record system, provided that the documents are retrievable.

13 Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval

- Risk Benefit Assessment

  The benefit of Aranesp is limited to a reduction in the risk of receiving allogeneic red blood cell transfusions and their attendant risks of transfusion-associated lung injury, infection, alloimmunization, as well as the cost and inconvenience of the transfusion procedure. Based on FDA's review of the information provided in the clinical study reports for the individual darbepoetin and epoetin alfa studies included in the analysis, there is no evidence based multiple studies in which patient-reported outcome instruments were used that demonstrated a quality-of-life benefit for cancer patients receiving an ESA as compared to placebo-treated patients. In addition, available data from randomized clinical trials do not indicate that use of an ESA provides an improvement in tumor-related outcomes, despite speculation on the existence of such benefits.

  This benefit in reduction in allogeneic transfusions is weighed against the risks of Aranesp (supported by data with Epogen/Procrit), which include increased mortality and shorter time-to-tumor progression in patients with cancer in whom ESAs were administered to target hemoglobin levels to normal or supraphysiologic level, and an increased risk of thrombotic events in all populations at recommended doses. Neither the risks of ESAs within patient populations defined by baseline hemoglobin at initiation of Aranesp or Epogen/Procrit in patients with cancer nor the benefits (reduction in the risks of RBC transfusion) are sufficiently well-characterized to provide accurate estimates either of these risks. However, as noted by Dr. Fan, the approval of the first epoetin alfa product occurred in an era where substantial concerns regarding the risks of transfusion, particularly the risks of transmission of HIV, Hepatitis B, and potentially other infections, existed. Since that time, the science of

transfusion medicine has advanced with resultant decrease in risks, while increasing evidence has been generated to support the previously theoretical possibility of adverse effects on tumor outcomes as well as poorer survival when ESAs are used to achieve high normal and supraphysiologic hemoglobin levels in patients with cancer and chronic renal failure. Thus, the risk-benefit profile has substantially changed over time.

In the absence of data clearly demonstrating harm at the currently recommended dose, with use limited to the indicated patient population, the risks have not been demonstrated to outweigh the benefits. This determination was based both on FDA review staff and advice received from members of the ODAC during the March 13, 2008 meeting. However, labeling must retain language included in product labeling following the March 2008 ODAC meeting which provide appropriate directions for use to minimize risks to subjects.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

  The license application for Aranesp is subject to a REMS under 505(o), originally approved under BL STN 10395/5195. The REMS has been modified under this supplement and the REMS assessment for consistency with revised labeling and to include revisions requested to minimize unnecessary burdens on end-users.

- Recommendation for other Postmarketing Requirements and Commitments

  No additional post-marketing requirements or commitments will be requested under this supplement.

SIGNATURES PAGE

/s/Patricia Keegan/ June 24, 2011

Patricia Keegan, M.D. Date
Director, Division of Biologic Oncology Products
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Center for Drug Evaluation and Research