Division Director Summary Review

Date	June 24, 2011
From	Patricia Keegan, M.D.
Subject	Division Director Summary Review
BLASupplement #	STN BL 103234/5166
Applicant Name	Amgen, Inc.
Date of Submission	December 26, 2007
Date of Re-Submission	October 26, 2009
Date of Re-Submission	March 23, 2011
PDUFA Goal Date	May 23, 2011
Proprietary Names / Established (USAN) Name	Epogen® and Procrit® epoetin alfa
Dosage Forms / Strength	Solution for subcutaneous or intravenous injection in single-use vials containing 2000 Units/1 mL, 3000 Units/1 mL, 4000 Units/1 mL, 10,000 Units/1 mL, or 40,000 Units/1 mL and in multidose vialscontaining 20,000 Units/2 mL or 20,000 Units/1 mL
Proposed Indication(s)	1. Treatment of anemia due to chronic renal failure (CRF) in patients on dialysis and not on dialysis to decrease the need for red blood cell (RBC) transfusion 2. Treatment of anemia due to zidovudine administered at ≤ 4200 mg/week in HIV-infected patients with endogenous serum erythropoietin levels of ≤ 500 mUnits/mL 3. Treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy 4. To reduce the need for allogeneic red blood cell (RBC) transfusions among patients with perioperative hemoglobin > 10 to ≤ 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery.
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Project manager generated minutes	Monica L. Hughes Mona Patel Ebla Ali Ibrahim
Medical Officer Reviews	Kaushikkumar Shastri Chaohong Fan Minh-Ha Tranh Saleh Ayache
Statistical Review	Kyung Yul Lee
Pharmacology Toxicology Review	Andrew McDougal Yanli Ouyang
CMC Review/OBP Review	Ingrid Markovic Kimberly Rains
Clinical Pharmacology Review	Aakansha Khandelwal
DDMAC	Iris Massucci (SEALD team) Carole Broadnax Cynthia Collins Michelle Safarik
OSE/DRISK	Melissa Hulett Amarylis Vega Sharon Mills
Pedatric & Maternal Health Consult	Richard Araojo

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Division Director Summary Review

1. Introduction

This efficacy supplement was submitted on December 26, 2007 as one of two supplements responding to FDA's supplement request letter of May 31, 2007. The May 31, 2007 letter made specific requests for revision to product labeling to enhance safe and effective use of Epogen/Procrit 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 103234/5158) addressing items 1, 2, and 6 of the May 31, 2007 and the "Prior Approval Supplement" (STN BL 103234/5166), which is the subject of this review, responding to items 3, 4, and 5 of the May 31, 2007 letter. The clinical study reports and an integrated dataset containing data from 23 randomized studies assessing the efficacy of Epogen/Procrit, Eprex, or Aranesp were provided in this supplement and in STN BL 103951/5173 for Aranesp, based on the rationale that the requested changes were considered class labeling. 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 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 to recommended use of Epogen/Procrit in an attempt to restrict the population to 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, and new study results demonstrating adverse outcomes in patients with chronic renal failure and in patients with cancer, as summarized below.

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. Amgen provided additional data on clinical trials (raw and select analysis datasets) for multiple trials, however these data were used only to support proposed labeling changes to the geriatric section of product labeling. In addition, non-clinical information on reproductive toxicology studies was provided in the resubmission was and incorporated into product labeling under sections 8 and 13. 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.

During the course of this review, as a result of 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. As part of the safety labeling changes, a Risk Evaluation and Mitigation Strategy (REMS) was approved on February 16, 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 STN BL 103234/5266, the first REMS assessment, which also contained proposed modifications to the REMS as well as additional proposed revisions submitted in an amendment (STN BL 103234/52566/5000) and a prior approval supplement containing the final report for, and proposed labeling revisions based on, the TREAT study, under STN BL 103234/5256. Agreement was reached on final labeling and modifications were made to REMS materials for consistency with the changes to the US PI, and for inclusion of the requested REMS modification and information based on the final report of the TREAT study. In addition, the concise REMS template was edited for consistency with current FDA policy regarding content and format of this document. 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. Epogen/Procrit (epoetin alfa) is produced in Chinese Hamster Ovary cells that have modified through recombinant DNA technology to encode the gene for human erythropoeitin. It was approved for marketing in the U.S. in 1988 for the treatment of anemia in patients with chronic renal failure based on the results of thirteen clinical studies that included a total of 1,010 patients. The application was supported by four additional studies in patients with renal failure whose disease was not severe enough to require dialysis and by pharmacodynamic and safety data from randomized, placebo-controlled six studies conducted in healthy males; 108 men received Epogen and 49 received placebo.

Epogen was subsequently approved for the treatment of anemia due to ziduvodine therapy in HIV-infected patients (1991) and for the treatment of anemia in patients with non-myeloid malignancies whose anemia is due to the effect of concomitantly administered chemotherapy (1993). These supplemental approvals were based on demonstration of a reduction in the proportion of patients receiving red blood cell (RBC) transfusions.

The labeling expansion to include a new indication for Epogen/Procrit for the treatment of anemia due to myelosuppressive chemotherapy for the treatment of cancer in 1993 was based on demonstration of a significant reduction in the proportion of patients receiving red blood cell transfusions from week 5 through the end of chemotherapy in pooled data from six randomized, double-blind, placebo-controlled trials enrolling 131 anemic patients with various solid tumors or lymphoid cancers, receiving either cisplatin-based (45%) or non-cisplatin-based (55%) combination chemotherapy.

There are two ESAs approved for the treatment of anemia due to chemotherapy in the United States, epoetin alfa (Procrit/ Epogen, Amgen Inc) and darbepoetin alfa (Aranesp, 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 Epogen/Procrit and Aranesp.

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 submitted on September 21, 2007 (STN BL 103234/5158) submitted on 19 September 2007. A CBE supplement was submitted for Aranesp on September 19, 2007 (STN BL 103951/5157). 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 103234/5166:

- STN/BL 103234/5164: 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 demonstrating adverse survival or tumor outcomes in patients with cancer receiving an ESA.

- (b) (4)
- STN BL 103234/5195 & 5196: Approval on November 19, 2008 of a Medication Guide (as ordered in FDA's April 22, 2008 letter) and of FDA-requested modifications to carton and container labeling
- STN BL 103234/5122: Approval on October 13, 2009 of revisions to 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 103234/5232: Approval on Jan. 11, 2010 of revisions to the Warnings section of the package insert to include the results of the TREAT study, a randomized, placebo-controlled study in anemic patients with diabetes and chronic renal failure not on dialysis which demonstrated an increased risk of stroke among patients randomized to ESA.
- STN BL 103234/5199: Approval on Feb. 16, 2010 of the REMS Program ordered under the April 22, 2009 letter under section 505-1 of the FD&C Act. Also approved were revisions to the package insert to refer to the REMS program in Dosage and Administration and Warnings sections and in the Medication Guide.

August 11, 2010 (STN BL 103234/5256) a prior approval supplement containing the final report for the TREAT and proposing revisions to the Indications and Usage, Warnings and Precautions, and Warnings section of the package insert..

October 15, 2010 (STN BL 103234/5266) first REMS assessment submitted. This document also contains proposed modifications to the describing proposed modifications to the ESA APPRISE Oncology Program Hospital Designee Enrollment Form and ESA APPRISE Oncology Program Website and an updated REMS Supporting Document

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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 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 protocols for two of the studies included in the integrated datasets, individual datasets for studies included in the integrated datasets and analyses, and SAS programs for derived variables.

- April 23, 2008: Amgen submitted revised labeling
- May 30, 2008: Amgen submitted additional responses to 3/7/08 letter
- June 16, 2008: Amgen submitted additional responses to 3/7/08 letter

March 28, 2008: FDA requested information

- Response received June 16, 2008

May 28, 2008: FDA issued letter noting that clinical study reports for multiple studies were incomplete with specific requests for missing information, requests for SAS programs to replicate specific analyses, requests for raw data and clarification of the approach to integrated safety analyses, sub-study reports on quality of life, and clarification of the methodology used to compile and analyze survival and tumor outcomes data.

- Response received Sept. 2, 2008

October 9, 2008: FDA provided Amgen with additional proposed labeling revisions, based on Amgen's labeling proposal of April 23, 2008
October 24, 2008: FDA issued a complete response letter

- Request for meeting to discuss CR letter received Jan 15, 2009
- Meeting cancelled on Feb 20, 2009 after receipt on Feb 13, 2009 of FDA draft responses to meeting questions

October 26, 2009: FDA received a class 2 re-submission, submitted October 23, 2009, responding to FDA's 10/24/09 CR letter. Included in the resubmission were

- A response document addressing each of the FDA's comments/requests identified in the 24 October 2008 FDA complete response letter.
- Revised labeling for Epogen and PROCRIT, including an annotated redline package insert, clean package insert, redline Medication Guide, clean Medication Guide, and labeling in structured product labeling (SPL) format.
- Information to support the revised labeling including:
  - A rationale document to support Amgen-proposed labeling modifications
  - Clinical study reports and datasets to support the geriatric update
  - Rationale documents and datasets to support revisions to the adverse drug
  - reactions tables
  - Reports to support safety-related labeling modifications
- A response document to address requests described in FDA's 28 May 2008 information request letter (STN BL 103234/5166) that were outstanding.

November 10, 2009: FDA acknowledgment of class 2 resubmission
January 12, 2010: Updated draft labeling (clean & redline) in PLR format incorporating the results of study 20010184 (TREAT) study.
January 15, 2010: Amgen submitted a labeling comparison table containing most recently approved Epogen PI incorporating TREAT stroke informationto h FDA's proposed labeling revisions sent in the Oct. 24, 2008 CR letter and Amgen's proposed labeling revisions as submitted on Jan. 12, 2010.
January 28, 2010: Amgen submission of an MS Word version of Epogen PIU for the resubmission
March 17, 2010: Amgen submission of establishment information
March 22, 2010: Amgen's response to FDA's proposed revisions of March 3, 4, and 10, 2010
March 23, 2010: Amgen submission in response to FDA information request for additional manufacturing site information from Amgen regarding ATO facility
April 12, 2010: Proposed REMS modification to incorporate changes to the Medication Guide and other REMS components necessitated by proposed labeling changes under this resubmission.
April 27, 2010: Complete response letter due to inability to reach agreement on product labeling.
Dec. 9, 2010: FDA contacted Amgen to discuss any issues and determine Amgen's plans for responding to the CR letter. As a result of this discussion, FDA met internally and provided advice to Amgen on revisions to product labeling to address inclusion of the TREAT results and proposed modifications to the Medication Guide on Jan 11, Feb. 16, Feb. 22, March 3, and March 16, 2011
March 23, 2011: Class Resubmission submitted.

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 and carton/container labeling were considered and incorporated into FDA proposed labeling which were conveyed to Amgen with the Oct. 24, 2008 CR letter. Amgen incorporated all FDA-request changes made under the original supplement review and there were no FDA-requested modifications to product labeling for the proposed labeling submitted in the resubmission. Under the CMC review of the resubmission, a Therapeutic Biologic Establishment Evaluation request was completed and identified no deficiencies which would preclude approval of this supplement. The CMC reviewer noted that approval of this supplement would not alter significantly the concentration or distribution of epoetin alfa or its degradation products, that Amgen complies with the categorical exclusion criteria listed in 21 CFR 25.31(c) and no extraordinary circumstances exist, therefore approval of categorical exclusion from environmental assessment was granted.

4. Nonclinical Pharmacology/Toxicology

No new non-clinical pharmacology or toxicology data were submitted in the original supplement, however FDA's oct. 24, 2008 CR letter, Amgen was asked to 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. In the resubmission, Amgen provided four

nonclinical study reports as text-searchable pdf files. The information (summary data) in these reports, previously submitted to the IND or BLA, supported Amgen's proposed language for the nonclinical pharmacology/toxicology sections of the label. All non-clinical reviewer comments regarding the package insert were considered and incorporated into FDA proposed labeling of March 4, 2010.

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 submitted in the original supplement for conformance with the PLR format, which were conveyed to Amgen with the Oct. 24, 2008 CR letter. The clinical pharmacology reviewer made additional editorial comments to section 7 and 12.3 of Amgen's proposed labeling in the resubmission and proposed wording to clarify section 6.3. All labeling comments regarding the package insert were considered and incorporated into FDA proposed labeling of March 4, 2010.

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 (epoetin alfa or darbepoetin 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.

- 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

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

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

A complete response letter was issued on October 24, 2008 notifying Amgen that missing information for 7 clinical studies was necessary to complete review. Amgen only provided data that were used in their analyses. FDA therefore asked for individual study specific data for all the studies used in combined analyses, requested during the original submission review and that were not provided for all the studies. Amgen was also asked to respond with labeling revisions or data in support of specific labeling statements. The October 26, 2009 resubmission provided the raw and selected analysis datasets for 7 studies identified in the initial submission as part of the pooled analysis dataset, thus a substantive review could be completed. This included raw and selected analysis datasets for Protocols CC-2574-P-174, EPO-INT-1, EPO-INT-2, EPO-INT-3, J89-040, CISPLATIN I88-036, 87-018, 87-019, and NON-CISPLATIN I88-037, 87-016, and 87- 017. The submission also provided the case report forms and safety narratives requested in the Oct 24, 2008 CR letter. Amgen noted that there was no new or additional safety information available for these clinical studies.

Amgen also provided revised labeling and a rationale document discussing the specific data supporting proposed labeling.

Study Identifier	Design	Total subjects (ESA : Placebo	Population	Hemoglobin entry criteria	Treatment Duration	Product Schedule	Hemoglobin "target"	Harmful Effects reported
I88-036, I87-018 I87-019	randomized placebo-control, parallel group	59 (28 : 31)	Anemia due to cancer and aggressive chemotherapy		12 wks	epoetin alfa TIW		N
I88-037 I87-016 I87-017	randomized placebo-control, parallel group	72 (35: 37)	Anemia due to cancer and aggressive chemotherapy		12 wks	epoetin alfa TIW		N
J89-040	randomized (2:1) placebo-control followed by open-label phase	221 (142: 79)	Patients with CLL	<32%	12 wks (blinded phase) 12 wks (open label)	epoetin alfa TIW	38-40%	N
CC2574-P-174[1]	randomized (2:1) placebo-control followed by open-label phase	45 (33:12)	Patients with CLL	<32%	12 wks (blinded phase) 12 wks (open label)	epoetin alfa TIW	38-40%	N
EPO-INT-1	Randomized dose-ranging (300 v 150 IU/kg) placebo-control, parallel group	246 (80:85:81)	Patients with ovarian cancer receiving platinum-based chemotherapy	<11 g/dL or ≥1.5-2 g/dL decrease from pre chemoRx baseline	12 wks	epoetin alfa TIW	12.5-14 g/dL	N
EPO-INT-2	randomized placebo-control followed by open-label phase	145 (69:76)	Patinets with multiple myeloma	<11 g/dL	12 wks (blinded phase) 12 wks (open label)	epoetin alfa TIW	-	N
EPO-INT-3	randomized (2:1) placebo-control followed by open-label phase	201 (136:65)	Patients with cancer receiving chemotherapy	< 12 g/dL or ≥1.5 g/dL decrease during chemoRx	12 wks (blinded phase) 12 wks (open label)	epoetin alfa TIW		

[1] "split off from J89-040 after accrual goals of J89-040 reached

Study Identifier	Design	Total subjects (ESA : Placebo	Population	Hemoglobin entry criteria	Treatment Duration	Product Schedule	Hemoglobin "target"	Harmful Effects reported
EPO-INT-10	Randomized placebo-control	375 (251:124)	Patients with cancer receiving chemotherapy		12 -24 wks during chemotherapy & 4 wks post-chemotherapy	epoetin alfa TIW		
PR98-27-008	randomized placebo-control	344 (174:170)	Patients with cancer receiving chemotherapy		16 wks	epoetin alfa QWK		
N93-004[2]	randomized placebo-control	224 (109:115)	Patients with small cell lung cancer	≤14.5 g/dL	During chemotherapy (3-6 cycles) & 3 wks post-chemotherapy	epoetin alfa TIW		
EPO-INT-7[3]6 (BEST)	randomized placebo-control followed by open-label phase	939 (469:470)	Patients with metastatic breast cancer receiving chemotherapy	<12 g/dL	12 months (blinded phase)	epoetin alfa QWK	12-14 g/dL	↓ OS
EPO-CAN-15	randomized placebo-control	104 (52:52)	Patients with limited stage small cell lung cancer		During chemotherapy & prophylactic cranial irradiation	epoetin alfa QWK		

[2] Terminated prematurely (after 224 of 400 planned subjects) due to poor accrual
[3] Terminated prematurely due to adverse effects on survival

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). Dr. Rothmann's summarization of these methodologic issues, as abstracted from his review, are reproduced below:

- 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.

In addition, as noted by Dr. Shastri, there are concerns with the pooling of the data across studies, even if statistical methodology for the presentation of survival data could have been addressed. Dr. Shastri's review points out the limitation of the individuals studies. Broadly, these limitations include the following:

- The hemoglobin entry criteria was in these studies does not reflect the current labeling and a substantial fraction, 28% or 814 of the 2890 patients in the pooled epoetin alfa dataset, had a baseline hemoglobin above 12 g/dL. However only one study stratified patients based on baseline hemoglobin level. Therefore, the composition of the subgroups are balanced or that the assumptions of random assignment hold within the subgroups as it does for the study overall.

- For most of the studies, there was no pre-specified plan for analysis of overall survival data, including the timing of the analysis, and the completeness of patient follow-up for survival is not assured.

- For most studies, there was no prospective plan for collection of vascular thromboembolic events (VTE) and the quality of the ascertainment and verification of the events is unknown.

Dr. Shastri also notes that drawing inferences about the starting hemoglobin levels or when to stop dosing based exploratory analyses of the per-patient incidence of transfusion overall and by hemoglobin subgroups using the pooled dataset are likely to be flawed due to the difference in design across studies. The studies used various hemoglobin entry criteria, different dosing and dose escalation criteria, were conducted in different population of patients and hence used different chemotherapy regimens with varying degrees of myelotoxicity, and had varying transfusion guidelines.

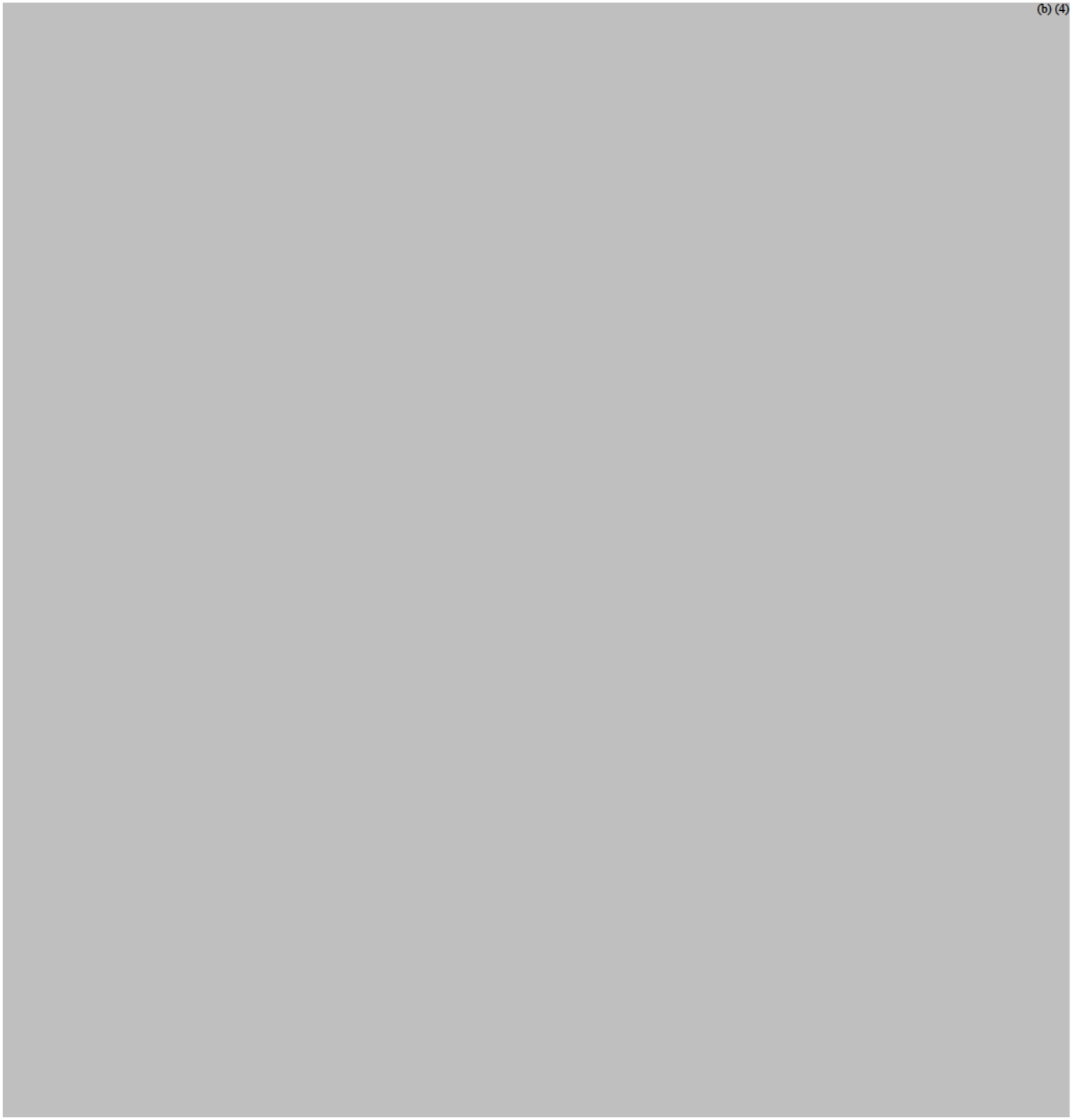
FDA Reviewers' assessment of Amgen's proposed labeling changes

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)



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*"

In their resubmission, Amgen did not propose any changes to the wording approved on August 5, 2008. However, the FDA's assessment of the original proposal is summarized below.

In his review, Dr. Shastri expressed reservations regarding the use of the pooled data as a means for identifying the appropriate dose for initiation of an ESA based on hemoglobin. He noted that the reduction in RBC transfusion rate was the greatest for subjects whose baseline hemoglobin level ≥9-10 g/dL (18%) and the absolute reduction in per-patient incidence of RBC transfusion was similar for subjects whose baseline hemoglobin levels ≥10-11 g/dL and ≥11-12 g/dL (13%) using the pooled dataset. However, the hemoglobin level subgroups of <9 and 9-10 showed larger absolute differences in transfusion rate between epoetin alfa and placebo in the analysis of individual studies. The reasons for differences between individual study results and the pooled analyses are not known. Regardless, the results of analyses within subgroups are 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).

For these reasons, and considering the advice of the March 2008 ODAC, FDA ordered safety language that for initiation of an ESA 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.

"The dose of EPOGEN/PROCRIT should be titrated for each patient to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for blood transfusion and not to exceed the upper safety limit of 12 g/dL"

Reduce Dose by 25% when:	*Hemoglobin reaches a level needed to avoid transfusion or increases > 1 g/dL in any 2-week period*
Withhold Dose if:	*Hemoglobin exceeds 12 g/dL and restart at 25% below the previous dose when the hemoglobin approaches a level where transfusions may be required"*

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 103234/5158) 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 epoetin alfa were: on-study death, death on follow-up, clinically relevant TVE, and progression-free survival (PFS). The outcomes were better for 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 for those who were treatment with epoetin alfa as well as for those who received placebo) for all but one comparison (clinically relevant TVE in patients receiving placebo).

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:

"Therapy should not be initiated at hemoglobin levels ≥10 g/dL...The dose of EPOGEN/PROCRIT should be titrated for each patient to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for blood transfusion.

Reduce Dose by 25% when:	*Hemoglobin reaches a level needed to avoid transfusion* *or* *increases > 1 g/dL in any 2-week period.*
Withhold Dose if:	*Hemoglobin exceeds a level needed to avoid transfusion. Restart at 25% below the previous dose when the hemoglobin approaches a level where transfusions may be required.*
Discontinue:	*If after 8 weeks of therapy there is no response as measured by hemoglobin levels or if transfusions are still required."*

The FDA-proposed labeling attached to FDA's October 24, 2008 CR letter was revised for brevity. The language, reproduced below, was largely accepted by Amgen in the resubmission:

"Dose Adjustment

- *Reduce dose by 25% if*
  - *hemoglobin increases > 1g/dL in any 2-week period or*
  - *hemoglobin reaches a level needed to avoid transfusion*

- *Withhold dose if*
  - *hemoglobin exceeds a level needed to avoid transfusion. Reinitiate at a dose 25% below the previous dose when the hemoglobin approaches a level where transfusions may be required.*

- *Discontinue if:*
  - *After 8 weeks of therapy there is no response as measured by hemoglobin levels or if transfusions are still required."*

FDA's assessment of the original proposal and rationale for counter-proposed language 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 statistcal 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 accepted this, however he also rejected Amgen's proposal based on more pragmatic grounds, which is that there is not basis to titrate treatment to achieve hemoglobin levels much above 8 g/dL given that "the sole indication for ESA administration is to reduce the need for transfusions. Most practitioners would transfuse at hemoglobin levels of 8 g/dL or below. There is no point in continue to administer ESA beyond the level needed to avoid blood transfusions, which certainly is not 12 g/dL. Many studies have shown adverse effects on tumor outcomes at higher hemoglobin levels, but these have not excluded harmful effects at a lower level. Hence it is only prudent to employ this supportive care agent for the purpose it is indicated for, i.e. reducing the need for blood transfusions. The placement of ceiling of 12 for withholding or discontinuing ESAs can lead to a wrongful assumption on part of practitioners that ESAs are safe when used up to a hemoglobin level of 12 g/dL."

I concur with the assessment of the clinical and statistical reviewers that Amgen did not provide adequate justification for retention of wording regarding an "upper safety limit of 12 g/dL". FDA has raised repeated objections to the validity of addressing the safety of a specific dosing regimen through pooled and meta-analyses. I agree that such approaches may assist in identification of safety signals, however I also note that confidence in the safety signals required multiple trials of appropriate design. As noted by Dr. Shastri, the ability to exclude risks is very difficult to do in this manner.

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:

(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 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"

In their resubmission, product labeling contained language consistent with the label approved on August 5, 2008.

The clinical and statistical reviewers did not review these data and referenced the findings of Drs. Fan and Shen regarding review of these data under STN BL 103951/5170, since the data were obtained in a trial that utilized Aranesp (darbepoetin alfa) rather than EPOGEN/PROCRIT.

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 epoetin 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. All clinical reviewer comments (see reviews by Drs. Kaushikkumar Shastri, Minh-Ha Tranh, and Saleh Ayache) regarding the package insert were considered and incorporated into FDA proposed labeling contained in the October 24, 2008 CR letter and in labeling provided to Amgen on March 4, 2010.

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.

Aside from reaching agreement on final labeling and modification to the REMS and REMS-related, elements to assure safe use documents, there are no additional unresolved regulatory issues.

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. Prior to the resubmission, a Medication Guide was approved, which replaced the patient packager insert. Thus review of the resubmission included review of the Medication Guide, which required modification due to FDA-proposed changes to the package insert. In addition, during FDA's review of the resubmission, a REMS was approved on Feb. 16, 2010 for EPOGEN/PROCRIT, which necessitated inclusion of references to the REMS in the physician package insert and Medication Guide.

In order to incorporate revisions to the Medication Guide, Amgen was directed to submit a REMS modification, which was received on April 12, 2010. Agreement on the language in the Medication Guide could not be reached due to failure to reach agreement on language in the package insert relating to the indication for anemia due to chemotherapy in patients with cancer. The areas of where agreement had not been reached for relating to the "cancer indication" included

- Boxed Warning
- Indications and Usage (1.3) and (1.5)
- Dosage and Administration (2.4)

Additional sections of the product labeling on which Amgen and FDA had not reached agreement are indicated on FDA's proposed labeling issued to Amgen on March 3, 4 and 10, 2010.

Amgen 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 both in the original submission and in the resubmission 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, as proposed both in the original supplement and in the resubmission. 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, submitted in the original submission and in the resubmission. 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

- [redacted] (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, some of which were based on labeling supplements approved during review of this application. The changes are briefly itemized below.

General changes:

- "adverse reactions" substituted for "adverse events" throughout labeling
- Changed language to active voice
- Added subsections to enhance identification of specific information
- Replaced symbols with descriptive wording

(1) Boxed Warning

In subsection on Chronic Renal Failure:

a. Replaced description of higher versus lower hemoglobin targets with "hemoglobin levels of 13 g/dL and above"

In subsections under Cancer Patients:

b. Deleted "when dosed to a hemoglobin target of ≥12 g/dL" since risks may be present with use of other targets (or with any exposure)

c. "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.

d. Added information on ESA APPRISE program
e. Added warning that ESAs are not included for patients with cancer who receive myelosuppressive chemotherapy with curative intent (e.g., adjuvant breast cancer) based on PREPARE results.
f. (b) (4)

In subsection on Perisurgery
g. Combined two sentences for brevity.

General changes
h. 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 multiple indications.
b. Currently approved indications statements re-worded for brevity and clarity. Information related to specific benefits limited (e.g., removed claim "to elevate or maintain RBC level" from the CRF indication or "increasing RBC level" under treatment of HIV infected patients) to specific benefit of reduction in RBC transfusion.
c. Titles of subsections shortened for brevity.

(3) Dosage and Administration

a. Extensively revised for brevity and re-worded for "active voice"
b. Added new subsection 2.1 on iron stores as a general instruction.
c. Included specific instructions for discontinuation of Epogen/Procrit for lack of efficacy under CRF, HIV, and cancer subsections.
d. Removed references to self-administration in Chronic Renal Failure section.
e. Removed text that duplicates information in other sections of labeling and replaced with cross-reference to relevant section (e.g., "lack or loss of response").
f. Added statement to "protect from light" based on evidence of photolability.

(4) Dosage Forms and Strengths

Information in this section moved to section 16 and section 11, as appropriate. remaining information shortened for brevity.

(5) Contraindications

a. Created specific subsection for contraindications limited to benzyl alcohol-containing formulations
b. Deleted contraindications based on theoretical risk of hypersensitivity to mammalian cell-derived products or to Albumin (Human) and replaced with specific contraindication based on prior serious allergic reaction to an ESA
c. Added Contraindications for PRCA secondary to an ESA

(6) Warnings and Precautions

a. Retitled section 5.1 and added "stroke" to the described adverse reactions; also added separate subsections for CRF, Cancer, and Surgery patients, to enshance legibility.

b. Added new study information under CRF patients subsection in 5.1

c. (b) (4)

d. Removed statement that ESAs are not approved for reduction of allogeneic RBC transfusions from the Surgery subsection of 5.1, as this is incorrect.

e. Addition of new section (5.2) relating to ESA APPRISE program

f. Edited title of section 5.3 to clarify population (cancer patients) and added "increased risk of recurrence). Edited for brevity through inclusion of cross-reference for information located in other sections of the label.

g. (b) (4)

h.

i.

j. 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)

k. 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.

l. (b) (4)

m. Section 5.4 (Hypertension) revised to delete unnecessary information on (b) (4) patients as this is not informative. Included essential information on dosing and advice to patients.

n. Edited sections on "lack or loss of response" for brevity. Referenced section 2 regarding recommendations for dosing in patients with inadequate response to treatment

o. Moved up "Seizures" to section 5.6 as next most common serious adverse event. Revised for brevity and active voice

p. Revised subsection on PRCA for brevity and active voice. Included information on risks of PRCA in patients with hepatitis C.

q. Retitled section on allergic reactions and moved down due to relatively low frequency of this event
r. Deleted subsection on Hematology. Relevant information now included in section on laboratory testing.
s. Subsection on Dialysis Management edited for brevity and critical information.
t. 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.

(7) Adverse Reactions

a. Extensively edited for brevity and for consistency with current FDA Guidance on Adverse Reactions section of product labeling. Additional data on patient demographics and dosing added to each section, for context.
b. Added reference to "serious allergic reactions" to bulleted list of serious adverse reactions.
c. Revised safety information under CRF subsection to distinguish between data from studies of patients on dialysis and data from studies of patients not on dialysis. Subheaders included to distinguish that information derived from studies in adults and from studies in children. Adverse reactions which were deemed probably related to ESA's in the judgment of the Div of Hematology reviewer were added to the adverse reaction table in this subsection. Separate adverse reaction tables provided for CRF patients on and not on dialysis Subsection on hypertension deleted as this is covered in other sections of the labeling and in the table.
d. Revised safety information from studies in HIV-infected patients to include adverse reactions which were deemed probably related to ESA's in the judgment of the Div of Hematology reviewer
e. (b) (4)
f. Adverse reactions described in tabular format for patients receiving Epogen/Procrit in the perisurgical setting revised to include only those events occurring more frequently in ESA-treated patients. Subsection on vascular/thrombotic events deleted as this is covered by the table and other sections of the labeling (e.g., 5.1).
g. Immunogenicity subsection edited to delete sentence "There has been no systematic assessment of immune responses…" as this is not informative

(8) Drug Interactions

Replaced "no evidence of interation of Epogen/Procrit with other drugs" with "No formal drug interactions studies have been conducted" for accuracy.

(9) Use in Specific Populations

a. Added information on risks to fetus/neonate with benzyl alcohol-containing formulations to the first part of this section to emphasize risks.
b. Pregnancy Category C: Provided data (from literature or other reports) on outcomes following exposure in pregnant women; Editorial changes describing

animal toxicology studies; Added reference to Amgen's pregnancy surveillance program

c. Nursing mothers: Added information on risks to fetus/neonate with benzyl alcohol-containing formulations to the first part of this section to emphasize risks Animal data in this section moved to Non-clinical toxicology section. This section modified in accordance with recommendations from Maternal-Fetal Health team.
d. Pediatric Use: Added information on risks to fetus/neonate with benzyl alcohol-containing formulations to the first part of this section to emphasize risks. Re-worded for clarity. Added information on pharmacokinetics in pediatric patients, where available with cross-references to Clinical Pharmacology (12.3) and Clinical Studies (14.1) added.
e. Geriatric Use: Updated this section to characterize the experience in geriatric patients across multiple studies in each indication. Editorial changes for clarity and consistency with applicable FDA Guidance.

(10) Overdosage

- This section was initially 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), subsequently limited to information on acute overdose only. Edited for brevity with deletion of non-essential information (e.g., information in Dosage and Administration on monitoring hemoglobin rate of rise).

(11) Description

- Updated to include detailed description (data moved from section 3 to section 11).

(12) Clinical Pharmacology

a. Section on Mechanism of action: The majority of this section was deleted because it refers to endogenous erythopoetin rather than Epogen/Procrit or is either covered in other sections (e.g., Clinical Studies).
b. Section on PD: Edited for brevity, essential information, and consistenty with applicable FDA policy, regulations, or Guidance.
c. Section on PK: Editorial changes to spell out acronyms. Deletion of "bioequivalence" statement for citrate- vs. phosphate-buffered formulations as irrelevant, since no clinically important PK differences were observed.

(13) Non-Clinical Toxicology

a. Subsections added under Carcinogenesis, Mutagenesis, and Impairment of Fertility. Substantial new infomraiton added on Impairment of Fertility based on non-clinical studies.
b. New section on Reproductive and Developmental Toxicology added. Includes some data previously described under Pregnancy subsection were moved to this new section; and new/expanded information on non-clinical reproductive toxicology findings added to this section as recommended by the nonclinical toxicology/pharmacology reviewer and the OSE consultant staff as the more appropriate section for these data.

(14) Clinical Studies

a. In general, section revised for brevity and clarity and to include appropriate clinical trial description in accordance with applicable FDA Guidance.
b. Clinical studies description re-organized to describe study design, give dose and exposure information first, then efficacy results in the CRF subsection (14.1). Results modified to included only the patients with efficacy data (mITT rather than ITT).
c. Reversed order of data presentation, with information on weekly dosing regimen in adults and pediatric patients (from Studies C1 and C2, respectively) presented first as this is regimen used in nearly all patients. Amgen asked to provide data on use of TIW regimen and whether the use is sufficient to retain information on this regimen in the label (both in sections 14 and 2).

(15) How Supplied and Handling Information

- Information previously provided in dosage forms and strengths moved to this section.
- Added information on storage/handling to protect from light.

(16) Patient Counseling Information

- Re-placed previous patient labeling with Medication Guide
- Bulleted to enhance legibility; revised for active voice.
- Added directions to advise patients of risks of thrombosis, increased mortality, tumor progression/recurrence, hypertension and seizures. Added instructions regarding need for and importance of routine laboratory monitoring and blood pressure monitoring. Noted when to contact healthcare provider (e.g., increased seizure activity, signs or symptoms of thrombosis).
- Added subsection for counseling of patients who are self-administering ;

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

- Editorial changes as recommended in by DRISK during labeling meetings

Additional labeling revisions and REMS Modifications incorporated during review of theCLASS 1 RESUBMISSION (103234/5166/ (b) (4), the REMS assessment and proposed modifications (103234/ 5266)

Physician Product Labeling

- **Boxed Warning**
  - Removed qualifier (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 Epogen/Procrit is not indicated for use [redacted (b) (4)] were replaced with Epogen/Procrit is not indicated for use "In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure. " and "Epogen/Procrit has not been shown to improve quality of life, fatigue, or patient well-being."
- **Dosage and Administration**
  - The term [redacted (b) (4)] 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.
  - Clarified instructions regarding preparation of single-use vials using bacteriostatic SWFI, USP
  - Added the information "Do not use Epogen/Procrit that has been shaken or frozen." to this section.
- **Dosage Forms and Strengths**
  - Minor editorial changes for brevity
- **Warnings and Precautions**
  - Changed title of subsection under Section 5.1, from "Surgery Patients" to "Patients Having Surgery" and edited information in this subsection for clarity.
  - Subsection 5.2: title modified to add name of drug, text modified to provide "command language" and for consistency with directions in REMS.
  - Revised description of analysis in Study 3 (under section 5.3) from "interim" to "final"
- **Adverse Reactions**
  - Removed information on [redacted (b) (4)]
- **Use in Specific Populations**
  - Moved detailed description of animal findings from 8.1 to section 13.3. Nonclinical information in 8.1 provided only in summary.
  - Editorial changes for brevity
- **Overdosage**
  - Replaced proposed labeling [redacted (b) (4)]

(b) (4)
(b) (4)
with

- **Description & How Supplied**
  - Deleted references to (b) (4)
- **Nonclinical Toxicology**
  - (b) (4)
- **Clinical Studies**
  - Deleted information on (b) (4) trial described under adult patients with CRF on dialysis, at recommendation of DMIHP reviewer.
  - Modification to characterize the efficacy population in C1, in whom the analysis of last-observation-carried-forward (LOCF) was used lack of data at the end-of-treatment period.

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
- Replaced statement (b) (4) with "These risks include that your tumor may grow faster and you may die sooner if you choose to take Epogen".
- Changes to confirm with revised Indications and Usage section in Physician Package insert
- Deleted (b) (4) as this should be based on the medical judgment of the healthcare provider and does not need to be in patient labeling.
- Added "Epogen has not been proven to improve quality of life, fatigue, or well-being." to address any misconceptions arising from direct-to-consumer ads.
- Replaced (b) (4) with Do not give Epogen from multidose vials to Pregnant or breastfeeding women or babies" for clarity

- Section on common side effects of Epogen/Procrit revised to remove (b) (4) as this is discussed in greater detail in the section immediately preceding on serious side effects of Epogen/Procrit. Discussion of (b) (4) under serious side effects no longer references (b) (4) as risks are not limited to this population.
- Information on risks to infants under "What are the possible side effects" have been expanded to describe that the risk is due to benzyl alcohol in specific formulations and to Epogen/Procrit and contains a description of the risks (e.g., brain damage).
- The listing of "common side effects" has been expanded.
- Bulleted list of inactive ingredients provided
- Information on presentations and formulations that are no longer marketed removed.

REMS template, supporting document, and website materials

- The concise 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 Epogen/Procrit is limited to a reduction in the risk of receiving a allogeneic red blood cell transfusions and the attendant risks of transfusion-associated lung injury, infection, alloimmunization, as well as the cost and inconvenience of the transfusion procedure. The risks of Epogen/Procrit, which include increased mortality and shorter time-to-tumor progression, appear to be increased with dosing strategies to achieve and maintain hemoglobin levels within the normal range. These risks have been observed both in patients with cancer and in patients with chronic renal failure. Neither the risks of ESAs nor the benefits (reduction in the risks of RBC transfusion) are sufficiently well-characterized to provide accurate estimates either of these risks. However, in the absence of data clearly demonstrating harm at the currently recommended dose, with use limited to the indicated patient population, the benefits outweigh the risks in patients with severe anemia who are transfusion-dependent (CRF patients) and anemic patients with other co-morbid conditions where exposure to ESAs are short (peri-surgical use) or in whom life expectancy is short (patients with cancer or

AIDS) This determination was based both on FDA review staff and advice received from members of the ODAC during the March 13, 2008 meeting.

As can be seen by Dr. Shastri's exhaustive review of the information provided in the clinical study reports for the individual 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 epoetin-alfa treated patients over placebo-treated patients.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

  Epogen/Procrit is subject to a REMS. The REMS minimizes risks to a requirement to ensure communication by the healthcare provider of specific risks, approved uses, and limitations of use for patients with cancer. Additional measures are not considered necessary at this time.

  Modifications have been incorporated in REMS materials for consistency with the approved package insert. In addition, the concise REMS template was modified for consistency with current FDA policy for such documents.

- Recommendation for other Postmarketing Requirements and Commitments

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

SIGNATURE PAGE

/Patricia Keegan/s/ June 24, 2011

Patricia Keegan, M.D. Date

Director, Division of Biologic Oncology Products