

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
103234Orig1s5166

MEDICAL REVIEW(S)

CLINICAL REVIEW ADDENDUM

Application Type sBLA
Submission Number 103234.5166
Submission Code PAS

Letter Date 3/22/2011
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PDUFA Goal Date 5/23/2011

Reviewer Name Kaushik Shastri, M.D

Through Patricia Keegan, M.D
Acting Team Leader &
Division Director

Review Completion Date 04/22/2011

Established Name epoeitin alfa
Trade Name Epogen/Procrit
Therapeutic Class Erythropoiesis Stimulating Protein
Applicant Amgen

Priority Designation Class 1 resubmission

Formulation Sterile colorless liquid in an isotonic sodium chloride/sodium citrate-buffered solution or a sodium chloride/sodium phosphate-buffered solution for intravenous or subcutaneous administration.

Dosing Regimen 40,000 units SC weekly or
150 units/kg SC three times/week

Indication Anemia due to myelosuppressive chemotherapy

Intended Population cancer patients with anemia due to chemotherapy

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1. Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends the approval of this supplement.

1.2 Risk Benefit Assessment

This is the second resubmission of this supplement, in response to a second CR letter issued on 4/27/10 for the original submission dated December 20, 2007. The CR letter was primarily due to lack of agreement on the labeling. This resubmission contains a package insert that is acceptable to the FDA.

A Risk Evaluation and Mitigation Strategy (REMS) was approved by the FDA on 2/16/10 under STN 103234/5199. With the already approved REMS, the risk/benefit assessment favors continued marketing of this drug for use in cancer patients with anemia due to myelosuppressive chemotherapy.

1.3 Recommendations for Postmarketing Risk Management Activities

A REMS program was already approved.

1.4 Recommendations for other Post Marketing Study Commitments

No other post marketing study commitment is recommended to this supplement.

2. Background and Overview

On 20 December 2007 (STN BL 103234/5166) Amgen originally submitted this prior approval supplement to revise the prescribing information and reformat according to the Physician Labeling Rule (PLR) and to respond, in part, to FDA's May 31, 2007 supplement request letter generated from questions raised and advice given at the May 10, 2007 ODAC meeting. The questions that were supposed to be addressed in this supplement included the threshold of baseline hemoglobin for the initiation of Epogen/Procrit, whether a lower (< 12 g/dL) hemoglobin level should be identified at which Epogen/Procrit should be suspended or terminated, and when to discontinue the use of Epogen/Procrit following the completion of the chemotherapy course. In the review of the Dec. 20, 2007 submission (see original review) it was determined that the submission did not contain robust evidence from studies sufficient to adequately address these issues. Subsequent label revisions that were approved following that Dec. 20, 2007 submission, have addressed the above issues with a conservative guidance for threshold of hemoglobin at which to initiate, suspend and terminate the use of Epogen/Procrit when treating cancer patients with anemia due to myelosuppressive chemotherapy. On 24 October 2008 FDA issued a complete response letter for this supplement since agreement on the labeling was not reached.

FDA issued a second CR letter on 4/27/10 since agreement on the final labeling again could not be reached.

During the later part of 2010 and earlier this year, FDA and Amgen conducted informal labeling negotiations and agreed upon the labeling language that is now submitted by Amgen in this second resubmission of this supplement.

This clinical review will only cover the Oncology portions of the submission, since the non-Oncology parts are being reviewed by Division of Hematology Products (DHP). This submission contains the necessary changes based on the agreed upon wording of the current label being approved with this supplement. The changes in the REMS are not a result of subsequent REMS assessment reports submitted by Amgen on 10/14/2011 and 2/16/11, since the content of these assessment reports did not by itself warrant changes to the REMS. Please see DRISK review of the REMS modifications.

3. Proposed Labeling Revisions (oncology portions) and Review Comments

As noted above, FDA and Amgen had informal discussions on the acceptable language of the physician package insert and this submission contains these changes.

Amgen essentially accepted all the FDA proposed changes in the label sent to Amgen on 16 March 2011 during informal labeling negotiations. For the Oncology portions of the label, these

changes are consistent with and vary only slightly from the proposed FDA label sent to Amgen with the CR letter on 04/27/10. The main issues are noted below:

Black Box Warning:

In the black box warning, under the first bullet under cancer, reference to the table 2 was added in the parenthesis as follows:

- ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers (Table 12, 5.3).

Review Comment: *Amgen had proposed that the sentence should qualify that these clinical studies were designed to achieve hemoglobin target ranges between 12 g/dL and >15 g/dL and argued that without such qualification they would have trouble explaining to the IRBs why they are doing the further studies (like the ongoing PMR studies) if the evidence is conclusive. FDA pointed out that the addition of the reference to the Table 2 from the Warnings and Precautions can be used to point to the actual data shown in Table 2 to articulate the scientific basis for the ongoing PMR clinical trials. Amgen's proposed wording may be misconstrued as implying that the drug is safe when given for lower hemoglobin levels.*

Section 1.2 Indication Statement:

(b) (4) 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. (1.2)

Review Comment: *The indication statement clarifies that at the time of initiation of (b) (4) for anemia due to myelosuppressive chemotherapy, there should be a plan to give the chemotherapy for at least two more months.*

Section 5.2: Prescribing and Distribution Program for (b) (4) in Patients with Cancer.
This section was revised for clarity.

Signature Page:



**Kaushik Shastri, MD
Clinical Reviewer,
DBOP**

Through:



**Patricia Keegan, MD
Acting Team Leader,
DBOP**

Summary Review for Regulatory Action

Date	April 27, 2010
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
PDUFA Goal Date	April 27, 2010
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 vials containing 20,000 Units/2 mL or 20,000 Units/1 mL
Proposed Indication(s)	<ol style="list-style-type: none"> 1. Treatment of anemia due to chronic renal failure (CRF) in patients both on dialysis and patients not on dialysis 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 that will be administered for a minimum of two additional months 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:	Complete Response

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
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
OSE/DRISK	Melissa Hulett
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, 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. As part of the safety labeling changes, a Risk Evaluation and Mitigation Strategy (REMS) was approved on February 16, 2010. Elements to assure safe use in the REMS will require modification as a result of the changes to product labeling under this supplement, however such changes cannot be made until agreement on product labeling is reached.

All reviewers concurred with FDA proposed labeling changes during labeling negotiations with Amgen however agreement on final labeling was not reached as of April 27, 2010. Thus a complete response letter was issued.

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 erythropoietin. 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 zidovudine 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 (b) (4) 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.

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 PROCRT, 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 information to 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.

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)	Patients 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). [REDACTED] (b) (4)

[REDACTED]

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

[REDACTED] (b) (4)

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 (b) (4)
 [Redacted] 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:

[Redacted] (b) (4) [Redacted]

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.

(b) (4)

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/PROCRIIT 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.

(b) (4)

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. (b) (4) 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. (b) (4)

[REDACTED]

The clinical reviewer noted that statisticians' assessment of the analyses and accepted this, however he also rejected Amgen's proposal (b) (4)

I concur with the assessment of the clinical and statistical reviewers (b) (4)

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

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 Tran, 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 (b) (4)

[Redacted]

- The addition of information on Study 20010145 to the WARNINGS AND PRECAUTIONS, Increased Mortality and/or Tumor Progression section (5.2) of the label. The proposed new language to be included in the label is reproduced below

[Redacted] (b) (4)

FDA Assessment: Both the clinical and statistical reviewer rejected (b) (4)

[Redacted]

- 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

[Redacted] (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 (b) (4)

[Redacted]

(b) (4)

- To add the information on Study N93-004 to the WARNINGS AND PRECAUTIONS, Increased Mortality and/or Tumor Progression section of the label. The proposed new language to be included in the label is reproduced below

(b) (4)

FDA Assessment: Both the clinical and statistical reviewer rejected

(b) (4)

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Complete Response
- 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 their 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. 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 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.

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. Modification to the REMS will be necessary to ensure consistency with the approved package insert. These changes cannot be made until agreement on the package insert is reached.

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.

- 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/
Patricia Keegan, M.D.
Director, Division of Biologic Oncology Products

April 27, 2010
Date

1 Page(s) has been Withheld in Full immediately
following this page as B6

Summary Review for Regulatory Action

Date	April 27, 2010
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
PDUFA Goal Date	April 27, 2010
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 vials containing 20,000 Units/2 mL or 20,000 Units/1 mL
Proposed Indication(s)	<ol style="list-style-type: none"> 1. Treatment of anemia due to chronic renal failure (CRF) in patients both on dialysis and patients not on dialysis 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 that will be administered for a minimum of two additional months 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:	Complete Response

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
OSE/DRISK	Melissa Hulett
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, 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. As part of the safety labeling changes, a Risk Evaluation and Mitigation Strategy (REMS) was approved on February 16, 2010. Elements to assure safe use in the REMS will require modification as a result of the changes to product labeling under this supplement, however such changes cannot be made until agreement on product labeling is reached.

All reviewers concurred with FDA proposed labeling changes during labeling negotiations with Amgen however agreement on final labeling was not reached as of April 27, 2010. Thus a complete response letter was issued.

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 erythropoietin. 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 zidovudine 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 (b) (4) 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.

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 PROCIT, 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 information to 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.

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)	Patinetes 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). [REDACTED] (b) (4)

[REDACTED]

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

[REDACTED] (b) (4)

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 (b) (4)

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.

(b) (4)

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.

(b) (4)

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. (b)(4) 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. (b)(4)

[REDACTED]

The clinical reviewer noted that statisticians' assessment of the analyses and accepted this, however he also rejected Amgen's proposal (b) (4)

I concur with the assessment of the clinical and statistical reviewers (b) (4)

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

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 Trinh, 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/PROCRT, 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 (b) (4)

[REDACTED]

- The addition of information on Study 20010145 to the WARNINGS AND PRECAUTIONS, Increased Mortality and/or Tumor Progression section (5.2) of the label. The proposed new language to be included in the label is reproduced below

[REDACTED] (b) (4)

FDA Assessment: Both the clinical and statistical reviewer rejected (b) (4)

[REDACTED]

- 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

[REDACTED] (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 (b) (4)

[REDACTED]

- To add the information on Study N93-004 to the WARNINGS AND PRECAUTIONS, Increased Mortality and/or Tumor Progression section of the label. The proposed new language to be included in the label is reproduced below

FDA Assessment: Both the clinical and statistical reviewer rejected

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Complete Response
- 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 their 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. 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 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.

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. Modification to the REMS will be necessary to ensure consistency with the approved package insert. These changes cannot be made until agreement on the package insert is reached.

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.

- 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/
Patricia Keegan, M.D.
Director, Division of Biologic Oncology Products

April 27, 2010
Date

1 Page(s) has been Withheld in Full immediately following this page as B6

CLINICAL REVIEW ADDENDUM

Application Type sBLA
Submission Number 103234.5166
Submission Code PAS

Letter Date 10/23/2009
Stamp Date 10/26/2009
PDUFA Goal Date 4/27/2010

Reviewer Name Kaushik Shastri, M.D

Through Patricia Keegan, M.D
Acting Team Leader &
Division Director

Review Completion Date 03/22/2010

Established Name epoetin alfa
Trade Name Epogen/Procrit
Therapeutic Class Erythropoiesis Stimulating Protein
Applicant Amgen

Priority Designation Class 2 resubmission

Formulation Sterile colorless liquid in an isotonic sodium chloride/sodium citrate-buffered solution or a sodium chloride/sodium phosphate-buffered solution for intravenous or subcutaneous administration.

Dosing Regimen 40,000 units SC weekly or
150 units/kg SC three times/week

Indication Anemia due to myelosuppressive chemotherapy

Intended Population cancer patients with anemia due to chemotherapy

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1. Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends the approval of this supplement with the with the FDA suggested revisions to the labeling submitted in the Physician Labeling Rule (PLR) format, medication guide and the patient instructions for use.

1.2 Risk Benefit Assessment

This supplement was originally submitted on December 20, 2007 to convert the label to Physician Labeling Rule (PLR) format and to address some of the issues raised at March 13, 2007 ODAC meeting for the use of Epogen/Procrit in anemic cancer patients, i.e. the threshold of baseline hemoglobin for the initiation of Epogen/Procrit and, a lower (< 12 g/dL) hemoglobin level at which Epogen/Procrit should be suspended or terminated. In the review of the original submission (see original review) it was determined that the submission did not contain robust evidence from studies to adequately address these issues. Subsequent label revisions that were approved following the original submission, have addressed the above issues with a conservative guidance for threshold of hemoglobin at which to initiate, suspend and terminate the use of Epogen/Procrit when treating cancer patients with anemia due to myelosuppressive chemotherapy. The physician package insert in this resubmission contains the conservative guidance for the use of this product already in the approved label.

During the course of the review of this resubmission a Risk Evaluation and Mitigation Strategy was approved by the FDA on 2/16/10 under STN 103234/5199.

The risk/benefit assessment with the already approved REMS favors continuing marketing of this drug for use in cancer patients with anemia due to myelosuppressive chemotherapy.

1.3 Recommendations for Postmarketing Risk Management Activities

A REMS program was already approved.

1.4 Recommendations for other Post Marketing Study Commitments

No other post marketing study commitment is recommended to this supplement.

2. Background and Overview

On 20 December 2007 (STN BL 103234/5166) Amgen originally submitted this prior approval supplement to revise the prescribing information and reformat according to the Physician Labeling Rule (PLR) and address some of the questions raised at the March 13, 2007 ODAC meeting. The questions that were supposed to be addressed included the threshold of baseline hemoglobin for the initiation of Epogen/Procrit, a lower (< 12 g/dL) hemoglobin level at which Epogen/Procrit should be suspended or terminated, and when to discontinue the use of Epogen/Procrit following the completion of the chemotherapy course. In the review of that submission (see original review) it was determined that the submission did not contain robust evidence from studies to adequately address these issues. Subsequent label revisions that were approved following that submission, have addressed the above issues with a conservative guidance for threshold of hemoglobin at which to initiate, suspend and terminate the use of Epogen/Procrit when treating cancer patients with anemia due to myelosuppressive chemotherapy.

On 24 October 2008 FDA issued a complete response letter for this submission since agreement on the labeling for the PLR conversion of the currently approved label was not reached. As noted above, the CR letter focused mainly on the PLR conversion of the label, since the sponsor did not conduct studies specifically designed to address the issues raised at the March 13, 2007 ODAC meeting and the more conservative dosing and administration guidance in the subsequently approved labels acknowledged the lack of studies to address those issues.

This re-submission contains Amgen's response to the FDA's complete response letter. This clinical review will only cover the Oncology portions of the submission, since the non-Oncology parts are being reviewed by another division (DMIHP).

Amgen has included in the submission the following in response to the items in the CR letter:

(1) Provided raw and select analysis datasets for studies CC2574- P-174, EPO-INT-1 (P416), EPO-INT-2 (P467), EPO-INT-3, J89-040 CISPLATIN: I88-036, 87-018, 87-019 and NON-CISPLATIN: I88-037, 87-016, 87-017. Amgen was also asked to provide case report forms and narrative summaries for all deaths and dropouts for studies CC2574- P-174, EPO-INT-2 (P467) and EPO-INT-3. Amgen has cited the location of the pages that contain the narrative summaries in the clinical study reports but not provided the case report forms. It is noted, however, that Amgen was specifically asked to provide these if they supported labeling changes based on the results of these studies. Amgen is only using the study J89-040 for geriatric labeling update and has proposed to add adverse reactions from the cis-platin and Non-cisplatin studies. This information is discussed in the adverse events section of this review.

2) Provided the source of the data used to derive the multiples of human exposure from the rat and rabbit reproductive toxicology studies (contained in Section 8.2 of the label). This is reviewed by the Toxicology reviewer.

3) Submitted response to comments embedded in the FDA proposed labeling sent with the CR letter. Specifically, the comments related to Oncology aspects of labeling was to verify the adverse events table in the label and demographics and stratification factor information in the Oncology studies in sections 6.1 and 14.3 of the label. In response to FDA's question if the three times/week dosing regimen is still used and asking Amgen to support their statement with utilization data, Amgen stated that the dosing regimen is still being used in clinical practice but they do not have detailed utilization data based on dosing regimen. The sponsor instead provided utilization data for the oncology indication as a whole, which does not address the question regarding specific dosing regimen.

4) Submitted a revised labeling.

5) through 11) The CR letter items concerned providing a safety update. In response Amgen stated that the 11 clinical study reports submitted in the original PLR submission provided all the available safety information for these studies; hence no additional safety information was provided. Regarding the summary of worldwide experience, Amgen stated that Epogen and Procrit are marketed in the US only.

3. Proposed Labeling Revisions, Supporting Data and Review Comments

The sponsor's proposed labeling revisions and the data supporting them as related to the oncology indication are discussed below:

(b) (4)

Reviewer Comments and recommendations: The adverse reactions data are derived from placebo-controlled studies and hence should retain the term adverse reactions.

(b) (4)

(b) (4)

Amgen proposes to include the following text in the label:

[Redacted text block] (b) (4)

[Redacted text block] (b) (4)

Update on Study Results in Section 5 Warnings and Precautions:

Since FDA has considered darbepoetin and epoetin alfa as belonging to the same class of Erythropoiesis Stimulating agents (ESAs) Amgen has incorporated the following updates in the Epogen/Procrit label for studies 20010103 and PREPARE.

As per Amgen, in the original submission, Amgen proposed a revision of description of the study 20010103 [Redacted text] (b) (4)

[Redacted text block]

The sponsor's red-line labeling revision of the OS results for study 20010103 is shown below:

[Redacted text block] (b) (4)

Review Comments: *This reviewer rejects the changes proposed by the sponsor. Please also see the statistical and clinical reviews for darbepoetin alfa (STN 103951.5173).* [Redacted text] (b) (4)

[Redacted text block]

PREPARE Study:

Amgen states that the current label reflects the interim analysis and the study is now complete and proposed the following change to the label:

[REDACTED] (b) (4)

Reviewer Comments and recommendation: Please see statistical review for detailed analysis of the updated data provided for darbepoetin alfa under 103951.5175. [REDACTED] (b) (4)

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED] Hence the proposed changes should be rejected.

Adverse Reactions Section (6.1):

Cancer Patients on chemotherapy:

Amgen was asked to verify the FDA generated adverse reaction table which included adverse reactions in Study C1 (PR98-27-008) that occurred with $\geq 5\%$ incidence in Epogen/Procrit treated patients and were also higher than those occurring in placebo treated patients.

Amgen verified the table but proposed that the following reactions be omitted from the adverse reactions table since they are likely to be confounded by chemotherapy or disease under study: nausea, vomiting, stomatitis, decreased weight, leucopenia, hyperglycemia, insomnia, hypokalemia, depression and dysphagia.

The sponsor's proposed the following for inclusion:

[REDACTED] (b) (4)

(b) (4)

Review Comments: Since this was a placebo controlled study it is not appropriate to exclude the adverse reactions. Hence the sponsor was asked to reinsert the following table (see review of the original submission).

Table 1: Adverse Reactions to Epogen in Cancer Patients on chemotherapy

Adverse Reactions to Epogen		
MedDRA (10,1) Preferred term	Epogen (n = 168)	Placebo (n = 165)
Nausea	35%	30%
Vomiting	20%	16%
Myalgia	10%	5%
Arthralgia	10%	6%
Stomatitis	10%	8%
Cough	9%	7%
Weight decrease	9%	5%
Leukopenia	8%	7%
Bone pain	7%	4%
Rash	7%	5%
Hyperglycemia	6%	4%
Insomnia	6%	2%
Headache	5%	4%
Depression	5%	4%
Dysphagia	5%	2%
Hypokalemia	5%	3%
Thrombosis	5%	3%

(b) (4)

The demographic information on the safety population is as follows:
 Table 2: Demographics of Safety Population:

Demographic and Baseline Characteristics Extracted from STUDY: PR98-27-008			
	PLACEBO (N=165)	PROCRIT (N=168)	Total (N=333)
Age			
N	165	168	333
Mean (SD)	63.8 (13.00)	63.5 (11.89)	63.6 (12.44)
Median	66.0	64.0	66.0
Range	24 - 86	20 - 88	20 - 88
Age group 1, n (%)			
N	165	168	333
Age < 65	75 (45)	85 (51)	160 (48)
Age >=65	90 (55)	83 (49)	173 (52)
Age group 2, n (%)			
N	165	168	333
Age < 75	126 (76)	138 (82)	264 (79)
Age >=75	39 (24)	30 (18)	69 (21)
Sex, n (%)			
N	165	168	333
Male	72 (44)	76 (45)	148 (44)
Female	93 (56)	92 (55)	185 (56)
Race, n (%)			
N	165	168	333
White/caucasian	146 (88)	158 (94)	304 (91)
Black	18 (11)	10 (6)	28 (8)
Hispanic	1 (1)	0	1 (<1)

The three times weekly dosing studies using Procrit represent pooled data from 6 different protocols and analyzed only 63 patients receiving Procrit and 68 subjects receiving placebo. Adverse reactions based on much larger study PR98-27-008 is appropriate and inclusion of (b) (4) is not necessary. Additionally, Amgen proposes to add the sentence (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

This reviewer therefore recommends removal of Amgen's proposed sentence [REDACTED] (b) (4)

Section 8.5 Geriatric Use:

To update the Geriatric Use section of the label, Amgen reviewed the studies across the 4 approved indications, besides the original approval studies, to determine if data from these studies would be appropriate for inclusion in the geriatric section of the labeling. The criteria used were 1) only studies of PROCIT®; 2) studies with at least 75 elderly subjects (ie, subjects >65 years), and 3) only randomized (for studies with more than 1 treatment group), controlled clinical studies. For oncology indication, the sponsor has identified the following 3 studies: N93-004, J89-040, and PR98-27-008.

Based on these studies, the sponsor proposes the following text:

Among 778 patients enrolled in the 3 clinical studies of PROCRT for the treatment of anemia due to concomitant chemotherapy, 419 received PROCRT and 359 received placebo. Of the 419 who received PROCRT, 247 (59%) were age 65 years and over, while 78 (19%) were 75 years and over. No overall differences in safety or effectiveness were observed between geriatric and younger patients. The dose requirements for PROCRT in geriatric and younger patients within the 3 studies were similar.

Reviewer Comments: The above addition to the geriatric section of the label is acceptable. The three studies cited were reviewed during the original submission. In review of this addendum, the sponsor's data were verified. Please also see the statistical review of this amendment.

The demographics for safety population are shown below

Table 5 : Demographics by Study and Age Category (Safety Population)

		All n, (%)	J89-040 n, (%)	N93-004 n, (%)	PR98-27-008 n, (%)
<65	Epo	172/419(41)	41/142(29)	46/109(42)	85/168(51)
	Control	159/359(44)	24/79(30)	60/115(52)	75/165(45)
≥65	Epo	247/419(59)	101/142(71)	63/109(58)	83/168(49)
	Control	200/359(56)	55/79(70)	55/115(48)	90/165(55)
<75	Epo	341/419(81)	104/142(73)	99/109(91)	138/168(82)
	Control	293/359(82)	61/79(77)	106/115(92)	126/165(76)
≥75	Epo	78/419(19)	38/142(27)	10/109(9)	30/168(18)
	Control	66/359(18)	18/79(23)	9/115(8)	39/165(24)

There was no difference between ITT population and safety population in studies J89-040 and N93-004. There are 11 more patients (6 patients in the epoetin alfa arm and 5 patients in the control arm) in the ITT population in study PR98-27-008.

The cumulative mean of Epogen exposures are summarized for age <65 vs. ≥65 and <75 vs. ≥75 by study using safety population.

Table 6: Cumulative Mean EPO Exposure by Study and Age Group (Safety Population)

		All	J89-040	N93-004	PR98-27-008
Total	Mean	497264(n=743)	321203(n=221)	402729(n=224)	698893(n=298)
	SD	289647	123221	290429	253815
<65	Mean	516671(n=318)	354517 (n=65)	422714(n=106)	656122(n=147)
	SD	283727	137155	286175	264475
≥65	Mean	482743 (n=425)	307322(n=156)	384776(n=118)	740530(n=151)
	SD	293493	114560	294252	236507

<75	Mean	500510(n=609)	336362(n=165)	415226(n=205)	686987(n=239)
	SD	285385	127625	290287	254446
≥75	Mean	482508(n=134)	276537 (n=56)	267895(n=19)	747119(n=59)
	SD	308973	97184	262672	247519

Although the cumulative mean epoetin alfa exposure varied across studies, overall there was no significant difference. The largest difference appears to be in age group <75 and ≥ 75 in study N93-004, but the study also had only 19 subjects ≥ 75 years old.

The demographics for the ITT population are shown below:

Table 7: Demographics by Study and Age category (ITT Population)

Age		All n, (%)	J89-040 n, (%)	N93-004 n, (%)	PR98-27-008 n, (%)
<65	Epo	172/419(41)	41/142(29)	46/109(42)	85/168(51)
	Control	159/359(44)	24/79(30)	60/115(52)	75/165(45)
≥65	Epo	247/419(59)	101/142(71)	63/109(58)	83/168(49)
	Control	200/359(56)	55/79(70)	55/115(48)	90/165(55)
<75	Epo	341/419(81)	104/142(73)	99/109(91)	138/168(82)
	Control	293/359(82)	61/79(77)	106/115(92)	126/165(76)
≥75	Epo	78/419(19)	38/142(27)	10/109(9)	30/168(18)
	Control	66/359(18)	18/79(23)	9/115(8)	39/165(24)

Table 8: Proportion of Patients Transfused After 28 Days by Study and Age Group (ITT Population)

		All n, (%)	J89-040 n, (%)	N93-004 n, (%)	PR98-27-008 n, (%)
Total	Epo	78/425(18)	43/142(30)	16/109(15)	19/174(11)
	Control	116/364(32)	40/79(51)	38/115(33)	38/170(22)
<65	Epo	31/175 (18)	13/41 (32)	6/46 (13)	12/88 (14)
	Control	49/162 (30)	13/24 (54)	23/60(38)	13/78 (17)
≥65	Epo	47/250 (19)	30/101 (30)	10/63 (16)	7/86 (8)
	Control	67/202 (33)	27/55 (49)	15/55 (27)	25/92 (27)
<75	Epo	66/346 (19)	36/104 (35)	13/99(13)	17/143 (12)
	Control	93/296 (31)	30/61 (51)	37/106 (35)	26/129 (20)
≥75	Epo	12/79 (15)	7/38 (18)	3/10 (30)	2/31 (6)
	Control	23/68 (34)	10/18 (56)	1/9 (11)	12/41 (29)

The overall relative risks of transfusion were fairly similar across the age group categories. There were very few patients in the ≥ 75 year age group in Study N93-004.

The incidence of adverse reactions in the overall safety population by age category is shown in the following tables.

Table 9: Incidence of Adverse reactions by age category of ≥ 65 and < 65 years

Preferred Term	% Incidence Procrit Age ≥ 65 N=247	% Incidence Procrit Age < 65 N=172	% Incidence Control Age ≥ 65 N=200	% Incidence Control Age < 65 N=159
	NAUSEA	32	45	28
FATIGUE	30	38	24	35
DIARRHOEA	20	19	12	23
VOMITING	19	31	19	22
CONSTIPATION	17	18	11	23
PYREXIA	16	9	5	14
ANOREXIA	15	17	11	17
ALOPECIA	14	27	17	22
ASTHENIA	12	9	6	13
GRANULOCYTOPENIA	12	17	11	12
COUGH	11	15	9	14
DYSPNOEA	11	14	9	24

Table 10: Incidence of Adverse reactions by age category of ≥ 65 and < 65 years

Preferred Term	% Incidence Procrit Age ≥ 75 N=78	% Incidence Procrit Age < 75 N=341	% Incidence Control Age ≥ 75 N=66	% Incidence Control Age < 75 N=293
	FATIGUE	26	35	35
NAUSEA	17	42	26	43
DIARRHOEA	15	21	23	23
ANOREXIA	14	16	15	20
PYREXIA	13	13	8	17
CONSTIPATION	12	19	23	24
COUGH	12	12	9	12
GRANULOCYTOPENIA	10	15	8	15
INSOMNIA	10	7	2	11
OEDEMA	10	7	12	7
PNEUMONIA	10	6	3	5
VOMITING	10	27	18	27

As shown, the incidence of adverse events was similar in the older population. There was a lower incidence of nausea and vomiting among older subjects than younger subjects in both the epoetin alfa subjects as well as the placebo subjects. It may reflect less aggressive dosing of chemotherapy for older subjects, as evidenced by a lesser incidence of alopecia in the ≥ 65 year age group in both the epoetin and the control arms compared to younger patients. This trend was present in each of the individual studies.

Labeling Changes related to REMS Approval:

Since this re-submission, a REMS was approved on 2/16/10. This necessitated changes in the product label to include information about the REMS program. This included the following additions:

Black box warning: *Prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology Program to prescribe and/or dispense Epogen to patients with cancer. To enroll in the ESA APPRISE Oncology Program, visit www.esa-apprise.com or call 1-866-284-8089 for further assistance [see Warnings and Precautions (5.2)].*

Section 2.3 Cancer Patients on Chemotherapy:

Only prescribers enrolled in the ESA APPRISE Oncology Program may prescribe and/or dispense Epogen [see Warnings and Precautions (5.2)].

Section 5.2

(b) (4)

Other Labeling Changes:

In addition to the above changes the label was revised for clarity. Those changes that pertain to the Oncology indication are summarized below:

Information in the black box warning was bulleted.

The indication and usage section in the highlight section and section 1.2 was revised to include the information that Epogen is indicated for treatment of anemia due to effects of concomitant myelosuppressive chemotherapy that will be administered for a minimum of two additional months in patients with non-myeloid malignancies.

The section on limitations of use was streamlined and bulleted.

The highlight section on adverse events in cancer patients was changed to reflect the changes in the adverse events section of the label.

Review of Medication Guide: (Note that Epogen and Procrit are the same drugs and carry identical package inserts, medication guides, and patient instructions for use; the reference to Epogen applies identically to Procrit).

The medication guide was revised to include information on the REMS program, update the adverse event information to be consistent with the PI, and streamlined for ease of reading.

Under "**What is the most important information I should know about Epogen?**" the following information was added.

[Redacted] (b) (4)

The statement that [Redacted] (b) (4) was modified to be consistent with the PI to include all patients including patients, including patients with cancer. The sentence now reads under the heading of All patients, including patients with cancer or chronic kidney failure: [Redacted] (b) (4)

Under '**what is Epogen?**' the following was added:

[Redacted] (b) (4)

Under '**Who should not take Epogen?**' the following information was added.

Do not take Epogen if you:

[Redacted] (b) (4)

The following sentences were simplified: [Redacted] (b) (4)

[Redacted]

The FDA proposed wording is as follows:

Do not give Epogen from multi-dose vials to:

- *Pregnant or breastfeeding women.*
- *Babies*

Under "**What should I tell my healthcare provider before taking Epogen?**" in the bullet beginning with 'Are pregnant or planning to become pregnant...the following was added:

If you are pregnant, discuss with your healthcare provider about enrolling in Amgen's Pregnancy Surveillance Program or call 1-800-772-6436 (1-800-77-AMGEN).

Under '**How should I take Epogen?**' a separate section for patients with cancer was created, which reads as follows:

Patients with cancer:

Before you begin to receive Epogen, your healthcare provider will:

- *Ask you to review this Epogen Medication Guide*
- *Explain the risks of Epogen and answer all your questions about Epogen*
-  (b) (4)

Under '**What are the possible side effects of Epogen?**', in the subheading of common side effects of Epogen, the following information was updated for consistency with the package insert:



Review of Patient Instructions for Use (PIU).

Please see DRISK review.

Under the heading '*When you receive your Epogen vial and syringes make sure that*', the following change was made:



Information about the different types of Epogen vials was rearranged and streamlined for ease of reading and the highlighting the difference between single dose and multi-dose vials. The following was added under the heading '*When you receive your Epogen vial and syringes make sure that*',

(b) (4)

Under the heading *What do I need to know about the different types of Epogen vials?*, the following information was added:

The Multidose-Use Vial of Epogen contains the preservative benzyl alcohol. Benzyl alcohol has been shown to cause brain damage, other serious side effects, and death in newborn and premature babies. Epogen that comes in single dose vials does not contain benzyl alcohol.

Under the heading of *'Intravenous route'*, the following change was made:

Epogen can be injected in your vein through a special access port- (b) (4) placed by your healthcare provider.

Under the instructions for disposing syringes and needles, disposition of vials was added. The modified portions of the section are as follows:

(b) (4)

Signature Page:

A handwritten signature in black ink, appearing to read 'K. Shastri', written in a cursive style.

**Kaushik Shastri, MD
Clinical Reviewer,
DBOP**

Through:

A handwritten signature in black ink, appearing to read 'Patricia Keegan', written in a cursive style.

**Patricia Keegan, MD
Acting Team Leader,
DBOP**

Summary Review for Regulatory Action

Date	October 24, 2008
From	Patricia Keegan, M.D. <i>PKeegan</i>
Subject	Division Director Summary Review
BLASupplement #	STN BL 103234/5166
Applicant Name	Amgen, Inc.
Date of Submission	December 26, 2007
PDUFA Goal Date	October 24, 2008
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 vials containing 20,000 Units/2 mL or 20,000 Units/1 mL
Proposed Indication(s)	<ol style="list-style-type: none"> 1. Treatment of anemia due to chronic renal failure (CRF) in patients both on dialysis and patients not on dialysis 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 that will be administered for a minimum of two additional months 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:	Complete Response

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including: Project manager generated minutes	Monica L. Hughes Mona Patel Ebla Ali Ibrahim
Medical Officer Reviews	Kaushikkumar Shastri Chaohong Fan Minh-Ha Tranh
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
OSE/DRISK	Melissa Hulett
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, 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.

All reviewers concurred with FDA proposed labeling changes during labeling negotiations with Amgen however agreement on final labeling was not reached. FDA will request additional information in support of proposed labeling changes or as justification for retention of current statements in the product labeling.

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 erythropoietin. 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 zidovudine 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 [REDACTED] (b) (4) [REDACTED] 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.
- [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]

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

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 are to be conveyed to Amgen in the CR letter.

4. Nonclinical Pharmacology/Toxicology

No new non-clinical pharmacology or toxicology data were submitted in the original supplement, however the CR letter will contain information requests from the nonclinical reviewer 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. 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.

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.

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 (b) (4)
- Proposed language, contained in earlier versions of product labeling but removed during previous labeling revisions, (b) (4)

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)	Patients 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). [REDACTED] (b) (4)

[REDACTED]

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

[REDACTED] (b) (4)

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 (b) (4)
 [REDACTED] 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:

[REDACTED] (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.

FDA reviewers completed their assessment of the rationale provided by Amgen in support of their initial proposals, which is summarized below.



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.

“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.

(b) (4)

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.”

Based on this action, Amgen’s proposed labeling language was replaced with the safety-ordered language. FDA will propose the following language, revised for brevity, in the labeling to be appended to the CR letter.

“Dose Adjustment

- *Reduce dose by 25% if
 - *hemoglobin increases > 1 g/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. (b) (4) 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 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. (b) (4)

[Redacted]

The clinical reviewer noted that statisticians' assessment of the analyses and accepted this, however he also rejected Amgen's proposal (b) (4)

I concur with the assessment of the clinical and statistical reviewers (b) (4)

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

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.

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/PROCRT.

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, and Minh-Ha Tran) 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. **Note:** 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. **Note:** 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.

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

(b) (4)

- The addition of information on Study 20010145 to the WARNINGS AND PRECAUTIONS, Increased Mortality and/or Tumor Progression section (5.2) of the label. The proposed new language to be included in the label is reproduced below

(b) (4)

FDA Assessment: Both the clinical and statistical reviewer rejected [REDACTED] (b) (4)

- 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

[REDACTED] (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 [REDACTED] (b) (4)

[REDACTED]

- To add the information on Study N93-004 to the WARNINGS AND PRECAUTIONS, Increased Mortality and/or Tumor Progression section of the label. The proposed new language to be included in the label is reproduced below

[REDACTED] (b) (4)

FDA Assessment: Both the clinical and statistical reviewer rejected [REDACTED] (b) (4)

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. [Redacted] (b) (4)

c. “adverse reactions” substituted for “events” throughout labeling.

(2) Indications and Usage section

a. New [Redacted] (b) (4) and “not indicated for” subsections created to limit repetition of the same information across multiple indications.

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

c. Titles of subsections shortened for brevity.

(3) Dosage and Administration

a. New [Redacted] (b) (4) subsection created to limit repetition of the same information across multiple indications.

b. Directions for patient monitoring deleted from this section to limit repetition; where necessary, such information is described under Warnings and Precautions (e.g., Hypertension, Laboratory Monitoring).

c. Elimination of redundant text (e.g., both text and table provide essentially the same dosing directions for patients with chronic renal failure).

d. Elimination of rationale for dosing directions (e.g., “response time of the hemoglobin to a dose increase can be 2 to 6 weeks”) or preparation and administration (e.g., prolonged vigorous shaking may denature...”).

e. References to [Redacted] (b) (4) deleted; these data are cited in context in the Clinical Studies section.

f. 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.

g. “maintenance dose” subsections deleted; information in these subsections generally overlap with information in the “dose adjustment” subsections, which were retained and re-worded for brevity and active voice.

(4) Dosage Forms and Strengths

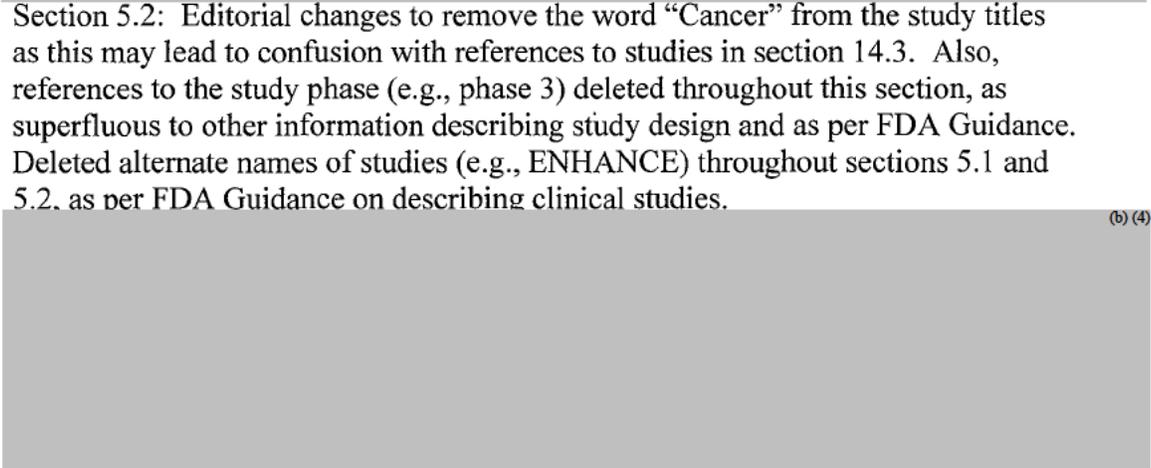
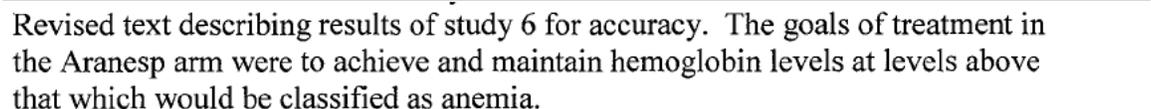
a. Information in this section moved to section 16; remaining information shortened for brevity and consistency with other labeling.

b. References to the [Redacted] (b) (4) deleted; [Redacted] (b) (4)

(5) Contraindications

- a. Replaced contraindication regarding theoretical allergic reactions to subcomponents with more specificity to serious allergic reactions as report in post-marketing experience and in Warnings/Precautions.
- b. Added contraindication regarding benzyl alcohol containing formulations in given the availability of an alternative formulation and consistent with proposed wordings in other sections not to use the benzyl alcohol containing formulation in pregnant women, neonates and infants due to documented risks with other products.

(6) Warnings and Precautions

- c.  (b) (4)
- d. 
- e. 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, references to the study phase (e.g., phase 3) deleted throughout this section, as superfluous to other information describing study design and as per FDA Guidance. Deleted alternate names of studies (e.g., ENHANCE) throughout sections 5.1 and 5.2. as per FDA Guidance on describing clinical studies.
- f.  (b) (4)
- g. 
- h. 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.
- i.  (b) (4)
- j.  (b) (4)
- k. Section 5.3 (Hypertension) revised to limit redundant dosing information that can be addressed with cross-reference to D&A section. Also deleted unnecessary information  (b) (4)

- l. Moved up “Seizures” to section 5.4 as next most common serious adverse event. Deleted statement “while the relationship between seizures and rate of rise...” as unnecessary explanation; dosing recommendations already adequately covered in D&A section of labeling.
- m. Deleted section on “loss of response”. Product labeling should not including information related to general practice of medicine (i.e., differential diagnosis and diagnostic work-up of anemia).
- n. Revised subsection on PRCA to remove references to deleted subsection on loss of response; edited for brevity and active voice.
- o. Deleted subsection on Hematology. First paragraph redundant and covered in subsection on laboratory monitoring and D&A. Second paragraph does not rise to level of “warnings” and has been edited for brevity and moved to the Adverse Reactions section of the label. The third paragraph is general medical information, unrelated to the product and therefore deleted from product labeling. The fourth paragraph was deleted as it relates to unapproved uses.
- p. Subsection on risk in infants deleted- superseded by new Contraindications statement
- q. Subsection on Dialysis Management edited for brevity and critical information; theories on potential effects and absence of effects in clinical studies deleted as unnecessary information.
- r. Subsection on (b) (4) 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. Analyses based on pooled datasets appear to underestimate effects observed in individual studies, thus these data have been deleted. Tables for individual studies should delete any rows in which events were more frequent in the control arm than placebo and remaining adverse reactions should be listing in decreasing incidence, based on rates in the Epogen arm.
- b. FDA cannot verify data in this table because SAS datasets not supplied (only program files). Please supply SAS transport files and a tabular summary of all adverse events.
- c. Hypertension subsection for patients with CRF deleted-to limit redundancy this information is now contained in the Warnings/Precautions subsection on hypertension.
- d. In the subsection on adverse events in cancer patients, data from the three-times-per week regimen across six studies was excluded because the small size and heterogeneity which may obscure safety signals and limit truly random allocation as well as the lower drug exposure when compared to the weekly dosing schedule.
- e. In the subsection on adverse events in patients scheduled for surgery, data on the SPINE study deleted to limit redundancy- these data are described in the new section 5.1
- f. Post-marketing section: Revised to include (b) (4) porphyria; this replaces section in precautions that contains no data on incidence and thus appears to be post-marketing reports. Revised section on allergic reactions for brevity and cross-reference more detailed information in the Warnings and Precautions subsection.

- g. Immunogenicity subsection: This section contains no data- please see FDA comments regarding provision of data or revision to state that data are not available from clinical studies.

(8) Drug Interactions

- Section revised to clarify that no drug-drug interactions studies have been performed/provided to FDA for this product.

(9) Use in Specific Populations

- a. Pregnancy Category C: Editorial changes. Added reference to Contraindications and information on risks of benzyl alcohol in premature infants.
- 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. Reference to Contraindications section added.
- c. Pediatric Use: Addition of reference to the Contraindications section and statement that benzyl-alcohol containing formulations should not be used in infants/neonates. Information on study in children with cancer deleted as this study is described in the Clinical Studies section (14). Re-worded for clarity.
- d. Geriatric Use: see FDA embedded comment regarding revision to reflect 5 clinical studies. Additional 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.

(11) Description

- a. Statement regarding “same biological effects as endogenous erythropoietin” deleted since this is already stated in the Clinical Pharmacology, mechanism of action subsection.
- b. Statement regarding source of endogenous erythropoietin production deleted as irrelevant to the manufactured drug.

(12) Clinical Pharmacology

- a. Section on Mechanism of action: The majority of this section was deleted because it is either covered in other sections (PD or PK subsections of clinical pharmacology or Clinical Studies subsections).
- b. Section on PD: Deleted redundant information in second sentence, first paragraph. FDA requests clarification of populations referenced in comment regarding failure to respond at doses of more than 300 U/kg three times per week.
- c. Section on PK: deleted comparisons of PK in CRF and healthy subjects as irrelevant. Re-worded comparisons of PK in CRF patients on and not on dialysis for clarity. Deleted comparisons of PK by formulation as irrelevant.

(13) Non-Clinical Toxicology

- 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.

(14) Clinical Studies

- a. In general, section revised to include appropriate clinical trial description in accordance with the Guidance for Industry document on this section of the label, including description of study population (demographics).
- b. Data should be limited to primary efficacy endpoints and data used by FDA as primary support to expand labeling claims (e.g., information in HIV-infected patients regarding lack of impact on HIV or other infections and on leukopenia deleted as irrelevant to determination of efficacy). Similarly, information on rate of hemoglobin increase in patients with CRF deleted because this information was not primary basis establishing efficacy in support of approval.
- c. Information on three-times-per-week dosing schedule in patients with anemia due to myelosuppressive chemotherapy deleted; use of this regimen is uncommon and the studies are less relevant in characterizing drug effects than the larger weekly dosing study which is retained in this section.

(15) How Supplied and Handling Information

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

(16) Patient Counseling Information

- Re-worded for ‘active voice’ and brevity.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Complete Response
- 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 their 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. 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 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.

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

The license application for Epogen/Procrit is subject to a REMS under 505(o). Agreement on language for the Medication Guide will proceed under a separate supplement.

- Recommendation for other Postmarketing Requirements and Commitments

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

CLINICAL REVIEW

Application Type sBLA
Submission Number 103234/5166
Submission Code PAS

Letter Date 12/20/07
Stamp Date 12/26/07
PDUFA Goal Date 10/25/08

Reviewer Name Kaushik Shastri, M.D.

Through Patricia Keegan, M.D.
Acting Team Leader &
Division Director

Review Completion Date 10/23/08

Established Name epoetin alfa
Trade Name Epogen/Procrit
Therapeutic Class Erythropoiesis stimulating agent
Applicant Amgen

Priority Designation S

Formulation

Sterile, colorless liquid in an isotonic sodium chloride/sodium citrate-buffered solution or a

sodium chloride/sodium phosphate-buffered solution for intravenous or subcutaneous administration.

Dosing Regimen	40,000 units SC weekly or 150 units/kg SC three times/week
Indication	Anemia due to myelosuppressive chemotherapy
Intended Population	cancer patients with anemia due to chemotherapy

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1 Recommendations/Risk Benefit Assessment

Recommendation on Regulatory Action

This reviewer recommends a complete response (CR) action be taken for this supplement since agreement on appropriate package insert is not reached. The CR letter will request Amgen to submit the revised labeling that incorporates FDA's proposed revisions and provide additional supporting information in the embedded comments in the label to be sent with the CR letter.

Risk Benefit Assessment

Since the approval of Epogen/Procrit in 1993, and Aranesp (darbepoetin alfa) in 2002 for treatment of anemia in cancer patients due to concomitantly administered chemotherapy, important safety signals pertaining to adverse tumor outcomes in patients receiving ESAs have emerged. These safety signals have led to convening of three Oncology Drug Advisory Committee (ODAC) meetings, where new information was discussed as it became available. Appropriate labeling changes were also made as and when new information became available. These ODAC meetings occurred in 2004, 2007 and 2008. The last revised label submitted by Amgen on August 5, 2008 as Changes Being Effected (CBE) adequately described the risks associated with ESA use and the benefits of ESA in terms of reduction of transfusion requirements in patients undergoing myelosuppressive chemotherapy. No new information on the risk and benefit considerations of Procrit use in the oncology setting was identified in this supplement.

Recommendations for Postmarketing Risk Management Activities

As described above, after the most recent ODAC meeting, on April 22, 2008, FDA issued a letter asking Amgen to submit a REMS for Epoetin alfa including, a Medication Guide, a communication plan for ensuring that healthcare professionals understand risks and benefits of Epoetin alfa, elements to assure safe use, an implementation system, and a timetable for assessment of the REMS. Amgen was also asked to conduct post-marketing studies to define the safety of Epoetin alfa related to tumor related outcomes. Amgen has submitted the REMS, which is under review. A draft protocol for post-marketing studies is under negotiations with the FDA.

Recommendations for other Post Marketing Study Commitments

None for this supplement.

2 Introduction and Regulatory Background

Product Information

Epoetin alfa (Epogen/Procrit) is a 165-amino acid glycoprotein manufactured by recombinant DNA technology. It has a molecular weight of 30,400 daltons and is produced by mammalian cells into which the human erythropoietin gene has been introduced. The product contains the identical amino acid sequence of isolated natural human erythropoietin.

Currently Available Treatments for Proposed Indications

Darbepoetin alfa (Aranesp) is the other erythropoiesis-stimulating agent marketed in the United States.

Availability of Proposed Active Ingredient in the United States

Epoetin alfa is currently marketed in the United States.

Important Safety Issues With Consideration to Related Drugs

FDA has considered adverse experiences with any of the erythropoiesis-stimulating agents as a class effect. Important safety issues of ESAs in the oncology setting include the increased risks for increased mortality, shorter time to tumor progression/recurrence, and increased incidence of thromboembolic events as described in the currently approved product labels of both Aranesp and Epogen/Procrit.

Summary of Presubmission Regulatory Activity Related to Submission

Since the approval of Epogen/Procrit in 1993, and Aranesp (darbepoetin alfa) in 2002 for treatment of anemia in cancer patients due to concomitantly administered chemotherapy, important safety signals pertaining to adverse tumor outcomes in patients receiving ESAs have emerged. These safety signals have led to convening of three Oncology Drug Advisory Committee (ODAC) meetings, where new information was discussed when available. Appropriate labeling changes were also made as and when new information became available. These ODAC meetings occurred in 2004, 2007 and 2008. This submission was requested by the FDA in a letter dated May 30, 2007 requesting Amgen to submit a prior approval supplement to address safety issues as discussed at the May 10, 2007 ODAC meeting.

Specifically, Amgen submitted this supplement primarily in response to the following items listed in FDA's May 31, 2007 letter:

1. **FDA Item 3:** *Revision of the INDICATIONS AND USAGE section to clarify the severity of anemia for which Epogen/PROCRT is indicated, by inclusion of the maximum, and if appropriate minimum, pretreatment hemoglobin level,*
2. **FDA Item 4:** *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, and*
3. **FDA Item 5:** *Revision of the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections to indicate that Epogen/PROCRT should be discontinued following the completion of the concomitant chemotherapy regimen.*

Other Relevant Background Information:

Since the submission of this supplement addressing the above issues, results of two additional studies became available showing adverse cancer outcomes, which led to another ODAC meeting to consider further limitations/restrictions on the use of ESAs in the cancer indication. Prior to the ODAC meeting, the label was revised on 3/7/08 to provide information on the new studies and included changes in the black box warning. During ODAC presentation, Amgen proposed a risk minimization strategy which included a proposal to request a change in the Dosage and Administration section of the label specifying that the hemoglobin level at which EPOGEN/PROCRT should be initiated is ≤ 10 g/dL. Following the ODAC meeting on March 13, 2008, the FDA issued a letter on April 22, 2008 under Title IX, Subtitle A, Section 901 of the FDAAA, requiring Amgen (a) to make safety related changes to the product labeling and proposed medication guide within 30 days of the letter, (b) Risk Evaluation and Mitigation Strategy (REMS) within 120 days of the letter, and (c) conduct postmarketing studies and provide a time table for milestones for the studies. Amgen submitted the revised label on 5/22/2008; this proposed label was the subject of further labeling negotiations. On July 30, 2008, FDA issued a labeling change order for unresolved issues under authority of section 505(o)(4)(E) of the FDCA. The order directed Amgen to make the changes to the label for the unresolved issues identified below: (1) In the Boxed Warnings and Indications and Usage sections, replace the statement, (b) (4)

(b) (4) with "Epogen/Procrit[®] is not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure." (2) Remove the following qualifying phrases (in italics) from the Dosage and Administration: Cancer Patients Receiving Chemotherapy subsection: a) *Therapy should not be initiated at hemoglobin levels ≥ 10 g/dL,* (b) (4)

b) *Withhold Dose if: Hemoglobin exceeds a level needed to avoid transfusion* (b) (4)

(b) (4). In response, Amgen incorporated the above changes and (b) (4)

http://www.amgen.com/medpro/epogen_pi.html for Epogen and
http://www.amgen.com/medpro/aranesp_pi.html for Aranesp.

In each of these labels, under Dosage and Administration subsection for the cancer chemotherapy indication it states the following: 'Therapy should not be initiated at hemoglobin levels ≥ 10 g/dL.' 'Discontinue following the completion of a chemotherapy course.' And under Dose modification it states " 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".

In summary, since receipt of this supplement for changes to the product label, there have already been two subsequent revisions to the label. The labeling issues (other than the conversion to PLR format) that were supposed to be addressed in this submission have since been revisited and revised in an acceptable manner in the current label.

3 Ethics and Good Clinical Practices

Submission Quality and Integrity

A Division of Scientific Investigations audit process was not employed to check the accuracy of the supportive data submitted by Amgen for this labeling supplement.

Most of the studies included for the combined analysis were more than 10 to 15 years old, and were not designed for the type of exploratory analysis that was submitted. 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, which Amgen has not yet provided for all the studies. Hence, in the complete response letter Amgen should be asked for individual study specific data, should they still want the data to support any labeling changes.

Compliance with Good Clinical Practices:

In individual study reports state that the study was carried in compliance with good clinical practices

Financial Disclosures

Amgen submitted FDA form 3454 signed by Amgen checking box 1 that states that Amgen has not entered into any financial arrangements with the listed investigators. In the list of clinical investigators is stated "see attached documents". The first attached document is reproduced below:

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS PROCRIT® (epoetin alfa)

Johnson & Johnson Pharmaceutical Research & Development, L.L.C. evaluated epoetin alfa studies included in this supplement with regards to the financial disclosure requirements. The PR98-27-008, EPO-INT-76 and EPO-CAN-15 studies were conducted on or after the implementation of financial disclosure regulations on 2 February 1998.

The PR98-27-008 study was a cooperative group study under the auspices of the National Cancer Institute for which financial disclosure information was not collected.

The EPO-CAN-15 study conducted with EPREX outside the US in 5 countries (34 sites) and enrolled 104 subjects. To the best of our knowledge none of the investigators had financial interests to disclose. Further, this study was terminated early due to an imbalance in thrombovascular events. In addition, no investigator enrolled more 11% of the total study population. As such, it is very unlikely that any one investigator influenced the overall results from this study.

The EPO-INT-76 study was conducted outside of the US in 19 countries (140 sites) and enrolled 939 subjects. None of the investigators had financial interests to disclose. In addition, no investigator enrolled more than 5% of the total study population. Based upon the multi-country and multi-center nature of this study, it is very unlikely that any one investigator influenced the overall results from this study.

Included in this section is the list of investigators for both the EPO-CAN-15 and EPO-INT-76 studies.

As noted in the above document reproduced from Amgen, the other attachments are simply list of investigators for Study EPO-CAN-15 with their names, site names and city and country names. For Study EPO-INT-76 the list has names and addresses of investigators, IRB names and addresses, names of subinvestigators and the number of patients enrolled per principal investigator/site.

Despite the lack of more complete information on financial disclosures, the submission contains studies that involved a very large numbers of investigators. The intent of the submission is to explore the data from these studies to derive a guideline for the hemoglobin level at which ESAs should be initiated and when the drug should be withheld or stopped. Besides the caveats of doing such exploratory analyses, there is very little chance of a bias from any financial conflict of investigators. The studies were not intended to be explored in this way when they were conducted.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Chemistry Manufacturing and Controls

No new information for CMC is submitted in this application. There are no outstanding CMC issues that can preclude approval of this supplement.

Clinical Microbiology

No information has been submitted in this supplement and is not applicable.

Preclinical Pharmacology/Toxicology

No information has been submitted in this supplement and there are no outstanding preclinical pharmacology/toxicology issues that can preclude approval of this supplement.

Clinical Pharmacology

No new information on the clinical pharmacology of epoetin alfa is contained this supplement. There are no outstanding clinical pharmacology issues that can preclude approval of this supplement.

5 Sources of Clinical Data

Tables of Clinical Studies:

Since darbepoetin alfa (Aranesp) and epoetin alfa (Epogen/Procrit) are both ESAs, FDA has always considered safety information related to one as applicable to the other as a class effect. In support of items covered in this supplement, besides the Aranesp studies (please see review of STN 103951.5173 by Dr. Fan), Amgen included clinical study reports or summary reports for the following epoetin alfa studies (this table is reproduced from Amgen's submission):

Table 1:

Type of Study	Study Identifier	Location of Study Report	Study Objectives	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy	88-036, 87-018/OE0-U24, 87-019/OE0-U25	Module 5.3.5.1	Efficacy and safety	Randomized, double-blind, placebo-control, parallel-group	Epoetin alfa: (PROCRIT) 150 IU/kg TIV/sc or placebo T IV sc	59: 29 epoetin alfa 31 placebo	Patients with anemia secondary to advanced cancer and aggressive cyclic chemotherapy	12 weeks	Complete; Summary report
Efficacy	88-037, 87-016/OE0-U22, 87-017/OE0 U23	Module 5.3.5.1	Efficacy and safety	Randomized, double-blind, placebo-control, parallel-group	Epoetin alfa: (PROCRIT) 150 IU/kg TIV/sc or placebo T IV sc	72: 35 epoetin alfa 37 placebo	Patients with anemia secondary to advanced cancer and aggressive cyclic chemotherapy	12 weeks	Complete; Summary report
Efficacy	89-040	Module 5.3.5.1	Efficacy and safety	Randomized, double-blind, placebo-controlled phase, followed by an open-label phase.	Epoetin alfa (PROCRIT or EPREX): 150 IU/kg TIV/sc or placebo T IV sc	221: 142 epoetin alfa 79 placebo	Patients with chronic lymphocytic leukemia	The double-blind phase of this study lasted 12 weeks and 12 weeks for open-label extension	Complete; CSR

Type of Study	Study Identifier	Location of Study Report	Study Objectives	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy	CC2574-P-174	Module 5.3.5.1	Efficacy and safety	Randomized, double-blind, placebo-control phase, followed by open-label and maintenance phases	Epoetin alfa (EPREX): 150 IU/kg TIV/sc or placebo T IV sc	45: 33 epoetin alfa 12 placebo	Patients with chronic lymphocytic leukemia	12 weeks double-blind phase, followed by 12 weeks open-label phase, followed by optional post open-label maintenance phase	Complete; CSR
Efficacy	EPO-INT-1/CC 2574-P-416	Module 5.3.5.1	Efficacy and safety	Randomized, double-blind, placebo-control, parallel-group	Epoetin alfa (EPREX): 300 or 150 IU/kg TIV/sc, or placebo TIV sc	246: 80 epoetin alfa 300 IU/kg 85 epoetin alfa 150 IU/kg 81 placebo	Patients with ovarian cancer receiving cyclic platinum based chemotherapy regimes	12 weeks	Complete; CSR
Efficacy	EPO-INT-2/CC 2574-P-457	Module 5.3.5.1	Efficacy and safety	Double-blind, placebo-control, followed by open-label extension	Epoetin alfa (EPREX): 150 IU/kg TIV/sc or placebo T IV sc	145: 69 epoetin alfa 76 placebo	Patients with multiple myeloma	12 weeks for double-blind phase, and 12 weeks for open-label extension	Complete; CSR

Table 1
 (continued)

Type of Study	Study Identifier	Location of Study Report	Study Objectives	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy	EPO-INT-3/CC 2574 P-034	Module 5.3.5.1	Efficacy and safety	Double-blind, placebo-control, followed by an open-label extension	Epoetin alfa (EPREX): 150 IU/kg TIV sc or placebo TIV sc	201: 136 epoetin alfa 65 placebo	Patients with malignancy receiving chemotherapy	12 week double-blind phase; and 12 weeks open-label extension	Complete; CSR
Efficacy	EPO-INT-10/EPO C111-467	Module 5.3.5.1	Efficacy and safety	Randomized, double-blind, placebo-control	Epoetin alfa (EPREX): 150 IU/kg TIV sc or placebo TIV sc	375: 251 epoetin alfa 124 placebo	Patients with anemia and cancer receiving chemotherapy containing chemotherapy	12 to 24 weeks or 3 to 8 chemo cycles, plus 4 weeks post-chemo	Complete; CSR
Efficacy	PR98-27-008 (NCCTG 97-92-53)	Module 5.3.5.1	Efficacy and safety	Randomized, double-blind, placebo-control	Epoetin alfa (PROCRT): 40,000 IU QW sc or placebo QW sc	344: 174 epoetin alfa 170 placebo	Patients with anemia and cancer undergoing chemotherapy	16 weeks	Complete; CSR
Efficacy	N93-004	Module 5.3.5.1	Efficacy and safety	Randomized, double-blind, parallel-group, placebo-control	Epoetin alfa (PROCRT): 150 IU/kg TIV sc or placebo TIV sc	224: 109 epoetin alfa 115 placebo	Patients with small cell lung cancer	At least 3 cycles of chemo, plus 3 weeks post-chemo.	Complete; CSR
Type of Study	Study Identifier	Location of Study Report	Study Objectives	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy	EPO-INT-76/BEST	Module 5.3.5.1	Efficacy and safety	Randomized, double-blind, placebo-control, followed by open-label extension	Epoetin alfa (EPREX): 40,000 IU QW sc or placebo QW sc	939: 469 epoetin alfa 470 placebo	Patients with metastatic breast carcinoma receiving chemotherapy	12 months, followed by open-label extension	Complete; Initial and long term follow up CSRs
Efficacy	EPO-CAN-15	Module 5.3.5.1	Efficacy and safety	Randomized, double-blind, placebo control	Epoetin alfa (EPREX): 40,000 IU QW sc or placebo QW sc	104 52 epoetin alfa 52 placebo	Patients with limited disease SCLC	Duration of chemo and through completion of PCI	Summary report

Review Strategy:

In addition to convert product label in a PLR (Physician's Labeling Rule) format, this submission centers around the following items identified in the FDA letter dated May 30, 2007 for revision of the package insert:

This submission centers around the following issues identified in the FDA letter dated May 30, 2007:

- (1) FDA item 3 of the letter: Revise the Indication statement to clarify the severity of anemia for which ESAs are indicated, i.e. pre-treatment hemoglobin level needed to initiate ESA therapy

(b) (4)

(2) FDA item 4 of the letter: Revise 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 (b) (4)

(3) FDA item 5 of the letter: Revise the Indications and Usage section and Dosage and Administration Section to indicate that ESAs should be discontinued following completion of concomitant chemotherapy regimen (b) (4)

It should be noted that since this submission, there has been two subsequent changes made to the label addressing the above issues satisfactorily. The latest revision to the label submitted by Amgen in a "changes being effected" (CBE) labeling supplement on August 5, 2008 states the following (1) therapy should not be initiated at hemoglobin levels ≥ 10 g/dL b) Withhold Dose if: Hemoglobin exceeds a level needed to avoid transfusion (3) discontinue ESA following completion of a chemotherapy course.

Nonetheless, Amgen's justification for the proposal regarding the above first two items is included in section 6 of this review. (b) (4)

In support of the first two items, Amgen provided exploratory combined subject level analyses of the results 11 studies utilizing epoetin alfa by reviewing the transfusion requirements at various baseline hemoglobin levels. Drawing inferences about the starting hemoglobin levels or when to stop dosing based on the composite analyses of such heterogeneous studies presents many obstacles. 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. The majority of studies did not have baseline hemoglobin as a stratification factor at the time of randomization. As discussed in section 6 of this review, focusing on the contribution of individual studies in drawing such inferences rather than combined analyses is more appropriate.

In discussion of individual studies, deficiencies in quality of life evaluations for these studies are also commented on.

Discussion of Individual Studies:

(1) EPO-INT-76 (BEST)

The results of this study are described in the currently approved label under Warnings and Precautions; (b) (4)

Amgen's proposal:

(b) (4)

(b) (4)

Study Title: A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Impact of Maintaining Hemoglobin Using Epoetin alfa (Epoetin Alfa; RWJJPRI-22512) in Metastatic Breast Carcinoma Subjects Receiving Chemotherapy.

Review Note: In this submission, Amgen provided a study report prepared by Johnson and Johnson Pharmaceutical Research & Development (J&J PRD) dated 16 April 2003 which has the study initiation date of 23 June 2000 and Study completion date of 5 July 2002. This report includes an addendum to the study report which used updated survival information from information collected from sites on the survival status of all subjects known to be alive as of last follow-up visit as of 04 January 2003. Amgen has also provided additional study report prepared by J&J PRD dated 26 Sept 2007 titled Open Label/Follow-Up study report which includes updated survival analysis based on follow-up information. The statistical review of the results from this last updated study report are included and discussed here where appropriate and are also discussed in detail in the statistical review (Please see Dr. Lee's review for this submission)

Objectives: The objective of this study was to evaluate the impact on survival and quality of life (QoL) of maintaining hemoglobin (Hb) in the range of 12 to 14 g/dL using epoetin alfa or placebo in subjects starting first-line chemotherapy for metastatic breast carcinoma.

Methodology: This was a Phase 3, double-blind, randomized, placebo-controlled, multicenter trial to evaluate the impact of maintaining hemoglobin (Hb) between 12-14 g/dL using epoetin alfa in subjects with metastatic breast cancer who were receiving first-line chemotherapy. A total of 939 subjects were enrolled in the study from 139 sites in 20 countries in Europe, Canada, South Africa, and Australia. Subjects were randomly assigned to receive either 40,000 IU epoetin alfa or placebo in a 1:1 ratio. Randomization was stratified by metastatic category (bone metastasis only versus other measurable metastatic lesions versus other non-measurable metastatic lesions) to ensure balance in the epoetin alfa and placebo arms. Study drug was administered once a week by subcutaneous (s.c.) injection to maintain Hb in the range of 12 to 14 g/dL for 12 months. Subjects could undergo a red blood cell (RBC) transfusion if clinically necessary during the study. Subjects who met the entry criteria were randomized, and study drug

was administered when Hb was 13 g/dL or lower. Hemoglobin concentrations and reticulocyte counts were monitored weekly for the first 4 weeks of the study to determine either when study drug administration was to begin or whether a dose adjustment was necessary. After the first 4 weeks of study drug administration, Hb concentrations and reticulocyte counts were monitored every 3 to 4 weeks for the remainder of the double-blind treatment phase. The maximum dose of epoetin alfa was not to exceed 60,000 IU once a week. After subjects had been on the study for 12 months, they completed the double-blind phase of the study and had the option of receiving 40,000 IU epoetin alfa once a week to maintain Hb in the range of 12 to 14 g/dL in an open-label extension. Efficacy was evaluated based on the primary endpoint of survival and secondary endpoints of hematologic effects, tumor response rates, time to disease progression, RBC transfusions, and quality of life (QoL). Safety evaluations were based on the incidence and severity of adverse events and the findings from clinical laboratory tests and vital sign measurements.

Diagnosis and Main Criteria for Inclusion: Subjects included in the study had a confirmed diagnosis of metastatic breast carcinoma, including histology of the primary tumor. Subjects were female, at least 18 years of age, were starting first-line chemotherapy for metastatic disease, had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2, and had a life expectancy of at least 6 months. Subjects were excluded if they had brain metastases or leptomeningeal disease at the time of randomization, if they were receiving dose intensification chemotherapy for bone marrow or stem cell transplantation, if they had an active second primary malignancy, or if there were causes of anemia known to be unresponsive to epoetin alfa.

Duration of Treatment: Duration of the double-blind phase was 12 months.

Number of Subjects (planned and analyzed): The planned enrollment was 870 subjects (435 subjects per treatment group). A total of 939 subjects (470 in the placebo group, 469 in the epoetin alfa group) were enrolled and analyzed in the intent-to-treat and safety populations (all randomized subjects), and 904 subjects (456 in the placebo group, 448 in the epoetin alfa group) were analyzed in the efficacy and modified safety populations (all randomized subjects who received at least 1 dose of study drug)

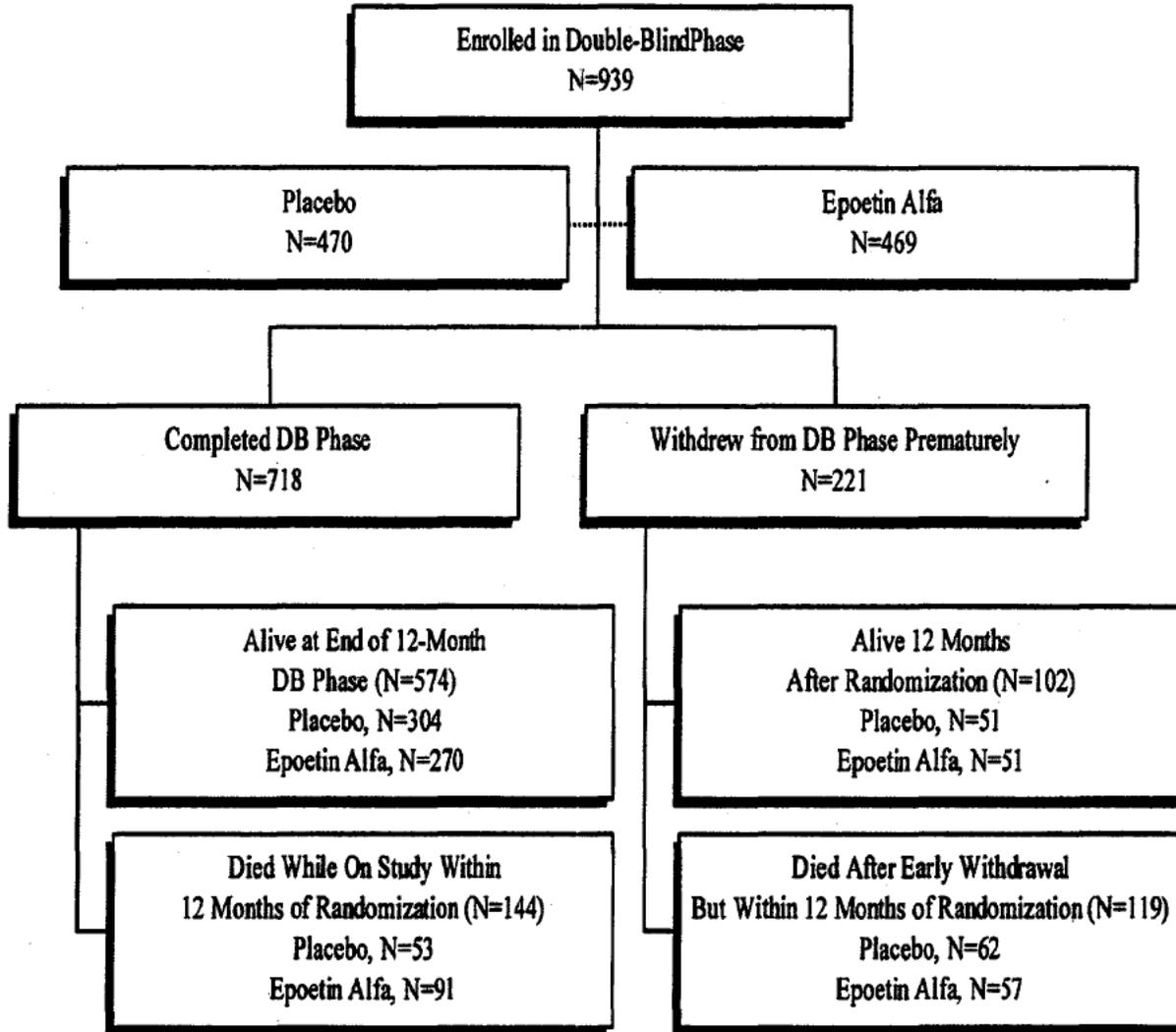
Criteria for Evaluation: **Efficacy:** The primary efficacy endpoint for the double-blind phase of the study was the 12-month survival rate, defined as the proportion of subjects surviving at 12 months after randomization. Secondary efficacy endpoints were change in Hb concentration from baseline to individual study end, Hb concentration over time, proportion of subjects receiving RBC transfusions from baseline to study end, standardized cumulative RBC units transfused from baseline to study end, optimal tumor response to first-line chemotherapy, tumor response at end of first-line chemotherapy, tumor response at the end of the study, time to disease progression, and QoL as measured by the Functional Assessment in Cancer Therapy-Anemia (FACT-An) and Cancer Linear Analogue Scale (CLAS) questionnaires. **Safety:** Evaluations were based on incidence of adverse events and changes from baseline in clinical laboratory tests and vital sign measurements.

Statistical Methods: Efficacy: Analysis of the primary efficacy endpoint was performed for the intent-to-treat and efficacy populations. The primary efficacy endpoint was the 12-month survival rate. Kaplan-Meier estimates of 12-month survival rate were presented by treatment group, and the hazard ratio, with its 95% confidence interval, were presented. Treatment comparison was made using the stratified (by metastatic category) log-rank test. The proportion of subjects receiving RBC transfusions was analyzed using a logistic regression model including metastatic status and treatment group as explanatory factors; the odds ratio and its 95% confidence interval, estimated by this logistic regression model, were provided. Possible treatment differences in optimal tumor response rates to first-line chemotherapy, and tumor response rate at double-blind study end, were analyzed using a stratified Cochran-Mantel-Haenszel test for ordinal responses. In addition, a proportional odds model for ordinal data was used to model the optimal tumor response data. Kaplan-Meier estimates of time to disease progression were presented by treatment group using the stratified (by metastatic category) log-rank test; the hazard ratio and 95% confidence interval were estimated using a stratified Cox's proportional hazards model. An exploratory post-hoc analysis of progression-free survival was performed using a similar approach. Quality of life data were analyzed using longitudinal techniques, and a mixed effects growth curve analysis was used to estimate the area under the QoL curve (AUCQoL) from randomization to Month 12. Sensitivity analyses were conducted based on different assumptions concerning the handling of missing data. Beyond testing for treatment differences in AUCQoL, the association between change in Hb concentration and QoL was examined using correlational techniques which also controlled for multiple comparisons. Safety: The percentage of subjects reporting adverse events was summarized by body system, preferred term, and included term. The severity of adverse events and relationship to study drug were summarized by body system and preferred term. Summary statistics (mean, standard deviation, median, and range) and changes from baseline were provided by treatment group for clinical laboratory tests and vital sign measurements.

Results:

Based upon an unblinded review of available data for 938 of the 939 randomized subjects which showed an apparent excess mortality rate in the epoetin alfa treatment group, the independent data monitoring committee (IDMC) recommended on 24 April 2002 that study medication be discontinued for all subjects. At the time of the IDMC's review, 179 deaths (101 in the epoetin alfa treatment group, and 78 in the placebo treatment group) had been reported in the double-blind phase of the study. The IDMC further recommended that all subjects, including those who withdrew from the study, continue to have study evaluations performed as described in the study protocol. J&J PRD agreed with the IDMC's recommendation and notified investigators and health authorities on 29 April 2002 that study medication was to be discontinued for all subjects. Subjects continued in the double-blind phase for its full 12-month duration. At the completion of the double-blind phase (or upon the 12-month anniversary of randomization for subjects who were withdrawn prematurely), subjects were to begin long-term follow-up evaluations which were to be performed every 3 months and included collection of survival information.

Figure 1: Patient Disposition:



NOTE: Completers were defined as subjects who completed the double-blind phase as per the investigator or who died with the date of death no later than the double-blind completion/withdrawal date. Withdrawals were defined as subjects who withdrew prematurely from the double-blind study and were alive on the date of withdrawal. Study medication was to be stopped for all subjects on 29 April 2002. 12 Months = Day 365 + 2-week window.

Table 2: Reason for Withdrawal:

	Placebo (N=470)		Epoetin Alfa (N=469)		Total (N=939)	
Lost to follow-up	9	(2)	14	(3)	23	(2)
Adverse event	22	(5)	16	(3)	38	(4)
Chemotherapy related	1		0		1	
Disease related	15		12		27	
Other	15		6		21	
Thrombotic/vascular event	4		6		10	
Missing	1		0		1	
Subject choice	41	(9)	41	(9)	82	(9)
Other	41	(9)	36	(8)	77	(8)
Missing	0		1	(<1)	1	(<1)

J&J PRD's Efficacy Results and Conclusions:

- Based upon the analysis of data using the 29 April 2002 cut off date, 265 subjects (116 placebo and 149 epoetin alfa) died within the first 54 weeks of randomization (25% for placebo, 32% for epoetin alfa). The treatment difference in survival rate was associated with a nominal p value of 0.0139 based on a stratified (bone metastasis only versus other metastatic disease) log-rank test without adjustments for other prognostic factors.
- The 12-month survival rate based on Kaplan-Meier estimates was lower in the epoetin alfa group (70%) compared to the placebo group (76%). The hazard ratio of Cox's proportional hazards model stratified by metastatic category was 1.37 (1.07, 1.74) (p=0.0112). The most common cause of death in both treatment groups was disease progression, accounting for 88% of all deaths in the intent-to-treat population during the 2-month double-blind study phase. For 6 (4%) subjects in the epoetin alfa group and 3 (3%) in the placebo group, the cause of death was related to thrombotic/vascular event.
- By comparison, mean hemoglobin levels were increased after Week 4 in the epoetin alfa group and remained at or elevated above the baseline level for the remainder of the study. The observed treatment group difference in hemoglobin levels over time, based on a linear mixed model, was statistically significant (p=0.0234).
- The proportion of subjects transfused from baseline to double-blind study end was lower in the epoetin alfa group (10%) compared to the placebo group (14%) (p=0.0595). The median pre-transfusion hemoglobin level for subjects who were transfused during the study was 8.3 g/dL in both treatment groups.
- The proportion of subjects in the complete response, partial response, stable disease, and progressive disease was not statistically different between the two treatment groups

($p=0.9303$) (46% in the placebo group and 45% in the epoetin alfa group showed a complete or partial optimal response to first-line chemotherapy).

- The percentage of subjects who showed progressive disease was similar for the two treatment groups (18% in the placebo group, 19% in the epoetin alfa group). Among the subjects who showed progressive disease, a higher percentage of subjects in the placebo group (67%) developed new lesions compared to the epoetin alfa group (49%).
- The tumor response at the end of first-line chemotherapy was similar for the two treatment groups (placebo (26%) and epoetin alfa (27%)).
- The tumor response at the last assessment for each individual subject during the 12-month double-blind phase was similar for the two treatment groups (placebo (46%) vs. epoetin alfa (42%)).
- The time to disease progression was comparable for the two treatment groups ($p=0.7059$). Based on Kaplan-Meier estimates, 43.4% of subjects in the placebo group and 41.1% of those in the epoetin alfa group had evidence of disease progression by Month 12.
- From J&J PRD's analyses, treatment of women with metastatic breast cancer with epoetin alfa or placebo for up to 12 months (54 weeks) had a similar effect on subjects' health-related QoL as reflected by changes in FACT-An and CLAS scores.

FDA Statistician's Review of J&J PRD's overall survival results based on the updated placebo cross over and long term follow-up information:

There were 715 deaths out of 939 subjects during the study in the updated data, 362 from the control group and 353 from the treatment group. The OS results for 54 weeks and for long-term follow-up in the updated data are summarized in Table below.

Table 3. Overall Survival (BEST)

Overall Survival	Epoetin Beta N = 469	Control N = 470
First 54 weeks		
Number of Patients With OS Event	149 (31.8%)	116 (24.7%)
Number of Patients Without OS Event	320 (68.2%)	354 (75.3%)
Median Duration of OS months (95% CI)	NE	NE
Hazard Ratio (95% CI)-unstratified		1.37 (1.07, 1.74)
P-Value (unstratified Log-Rank Test)		0.0112
Hazard Ratio (95% CI)- stratified*		1.36 (1.06, 1.73)
P-Value (stratified Log-Rank Test)		0.0139
Updated data for long-term follow-up		
Number of patients with OS Event	353 (75.3%)	362 (77.0%)
Number of Patients Without OS Event	116 (24.7%)	108 (23.0%)
Median Duration of OS months (95% CI)	20.96 (19.29, 23.75)	22.05 (19.58, 25.03)
Hazard Ratio (95% CI)-unstratified		1.05 (0.90, 1.21)
P-Value (unstratified Log-Rank Test)*		0.5370
Hazard Ratio (95% CI)-Stratified		1.04 (0.89, 1.20)
P-Value (Stratified Log-Rank Test)*		0.6411

*Stratification factors are metastatic category (bone metastasis only versus other measurable metastatic lesions versus other non-measurable metastatic lesions)

In the double blind phase (one year OS), 116 (24.7%) subjects in the placebo group and 149 deaths (31.8%) in the epoetin alfa group had died.

After the double-blind phase of 12 months 94 subjects from the epoetin alfa group and 134 subjects from the placebo group were enrolled in the open-label phase and received epoetin alfa by a subcutaneous route of administration at a starting dose of 40,000 IU each week.

The number of patients who enrolled in the open-label (OL) phase after the double-blind phase was 228 patients in the updated open label profile data set.

Table 4. Number of Deaths in the Double Blind Phase and Open Label Phase

	Double blind	Open Label Phase (OL)	
		Epoetin alfa (%)	No OL (%)
<i>Epoetin alfa</i>	149/469 (31.8)	77/ 94 (81.9)	276/375(73.6)
<i>Placebo</i>	116/470 (24.7)	98/134 (73.1)	264/336 (78.6)
<i>Total</i>	265/939 (28.2)	175/228 (76.8)	540/711(75.9)

Four patients who were listed as dead in the original analysis, had their survival times changed in the updated analysis. Those four patients were dead in both analyses, but in all instances their times to death decreased.

Table 5: Disparity in the Time of Death

Patient ID	Treatment group	Original times to death	Updated time to death
EPO-CA-489-CDN05-1009	Epoetin Alfa	500	491
EPO-CA-489-PL06-3112	Placebo	456	453
EPO-CA-489-PL01-3159	Epoetin Alfa	309	302
EPO-CA-489-PL07-3217	Placebo	341	314

Review Comments regarding Amgen's proposal for labeling updates:

(b) (4)
[Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted] Inferior overall survival for the first 54 weeks was demonstrated in the epoetin alfa arm and this information is included in the current label.

Additional review comments:

Since this study had a hemoglobin entry criteria well beyond the labeled indication, this study is not useful in arriving at the optimal hemoglobin initiation level or at what hemoglobin level (<12 g/dL) to withhold or discontinue epoetin alfa. In addition to the caveats of the instruments used, the study did not show a difference between the treatment arms on subjects' health-related QoL as reflected by changes in FACT-An and CLAS scores. However, the analyses ignored that overall survival was inferior for epoetin alfa for the first 54 weeks (patients who died during the first 54 weeks were not included in the QoL analysis).

(2) Study N93-004

This study was conducted as a post-marketing commitment (PMC). It was reviewed previously by FDA as a PMC final study report. (b) (4)

[Redacted]
[Redacted]
[Redacted]

Study Title: The Effect of r-HuEPO in Patients with Small Cell Lung Cancer (SCLC): A Randomized, Double-Blind, Placebo-Controlled Trial

Study Initiation/Completion Dates: 15 July 1993 - 06 May 2002. The study was prematurely terminated for poor recruitment on 17 July 2001.

Objectives: This study was undertaken by J&J PRD as part of post-approval commitment to the original approval for Epogen/Procrit for treatment of anemia due to cancer chemotherapy. The study was intended to evaluate for possible stimulatory effects of epoetin alfa on solid tumor growth. The primary objective of this study was to determine the effect of epoetin alfa on tumor response in SCLC subjects receiving therapy with VP-16 (etoposide) and cisplatin. The secondary objectives were to evaluate the effect of epoetin alfa on survival, erythroid parameters, and transfusion rate in SCLC subjects.

Methodology: This Phase 4, randomized, double-blind, parallel group, placebo-controlled trial was conducted at 35 sites in the United States. At the time the study was initiated, the standard treatment regimen for SCLC consisted of etoposide and cisplatin. Since that time, the standard of care for SCLC evolved from that which was specified in the protocol. As a result, recruitment into the study was slow and the study was terminated prematurely, with FDA agreement, after 224 subjects had been enrolled and completed the double-blind treatment phase. This Phase 4 study consisted of a double-blind treatment phase with up to 12 cycles of chemotherapy followed by 3 years of double-blind follow-up for assessment of survival. Subjects scheduled to begin a course of chemotherapy with etoposide and cisplatin for newly diagnosed SCLC were randomly assigned in a 1:1 ratio to receive either epoetin alfa 150 IU/kg or placebo, given subcutaneously (s.c.) three times a week (t.i.w.), until approximately 3 weeks after completing the final cycle of chemotherapy. Etoposide/cisplatin chemotherapy was to be administered every 3 weeks for at least 3 cycles. The recommended starting dose of etoposide was 100 mg/m² on Days 1-3 of each cycle, while the recommended starting dose of cisplatin was 100 mg/m² during each cycle (generally on Day 1), although the dose and schedule could have been varied as needed based on toxicity. No other chemotherapeutic agents were permitted during the study, and non-palliative radiotherapy was prohibited during the first 3 cycles. Approximately 3 weeks after Cycle 3 and after the completion of the final cycle, the extent of measurable and evaluable malignant disease was determined by the appropriate imaging techniques. Ratings of disability, using the Eastern Cooperative Oncology Group (ECOG) performance status score, were made at baseline and at study completion/termination. A blood sample was obtained for determination of hematology

parameters immediately prior to administration of the chemotherapy regimen on Study Day 1 and weekly thereafter until 3 weeks after completion of the final cycle of chemotherapy. A serum chemistry profile and urinalysis were to be performed prior to initiation of each cycle of chemotherapy and approximately 3 weeks after completion of the final cycle of chemotherapy, and iron status (serum iron, ferritin and total binding capacity) were evaluated at screening and at the final visit. Adverse events and vital signs were monitored throughout the study. Information about subjects' survival status was obtained annually for up to 3 years after study completion. Although annual follow-up was not collected consistently in this way, J&J PRD retrieved post-study survival information from the sites prior to study completion.

Number of Subjects (planned and analyzed): 400 planned; 224 enrolled and analyzed.

Diagnosis and Main Criteria for Inclusion: Subjects were to be ≥ 18 years of age with newly diagnosed, histologically-documented, measurable and evaluable, limited- or extensive-stage SCLC and scheduled to begin chemotherapy with etoposide and cisplatin. Subjects were not to have received prior cytotoxic chemotherapy or radiotherapy, were to have a life expectancy of at least 3 months, and were to have a baseline hemoglobin level of ≤ 14.5 g/dL.

Duration of Treatment: At least 3 cycles of chemotherapy, plus 3 weeks post-chemotherapy.

Criteria for Evaluation: Efficacy: The primary efficacy endpoint was the proportion of subjects in each treatment group who had a complete (complete absence of detectable tumor) or partial (reduction in estimated tumor mass by $\geq 50\%$ and no new lesions) response to chemotherapy after the third cycle of chemotherapy. Secondary endpoints included survival rate, the proportion of subjects with a complete or partial response after the final chemotherapy cycle, changes in hemoglobin levels over time, red blood cell (RBC) transfusion rates on-study, and the ECOG performance status scores at baseline and the final visit. **Safety:** Safety evaluations included assessments of the incidence and severity of adverse events, changes in clinical laboratory tests, changes in vital sign measurements, and physical examination abnormalities.

Original Sample Size calculations:

The following paragraph appears in the study protocol: "The sample size is determined so that there is high power of detecting a specified "minimum detectable reduction" in the proportion of patients whose tumors respond to therapy (overall response i.e. complete response or partial response) after three cycles of chemotherapy. For purposes of this protocol this reduction is taken to be 15% and the overall response rate in the placebo group is taken to be 60%. Given a power of 90% and a significance level of 0.05 (one-sided), the sample size needed to detect a reduction of 15% is approximately 190 per treatment arm. Allowing for a dropout rate of 5%, 200 patients will be enrolled in each treatment arm based on the arcsine approximation to the binomial"

Statistical Methods: Because the study was terminated prematurely for poor recruitment after 224 of the target 400 subjects had been enrolled, analyses of efficacy endpoints consisted of descriptive summaries. The percent of subjects with an overall tumor response (complete plus partial) and 95% confidence interval (CI) at the end of Cycle 3 and after the final chemotherapy

cycle was calculated by treatment and stage of disease at diagnosis. The observed difference in overall tumor response rate (epoetin alfa minus placebo) and 95% CI were calculated; the primary objective was to show that overall tumor response rate in the epoetin alfa group was not 15% below that in the placebo group after 3 cycles of chemotherapy. Kaplan-Meier estimates of survival over the entire course of the study and follow-up were generated as a function of treatment and stage of disease at diagnosis. Kaplan-Meier estimates of an on-study transfusion were also generated for each treatment group.

Demographics: Demographic characteristics of the 2 treatment groups were similar. Of the 224 enrolled subjects, most (86%) were white, 55% were men, and the mean age was 63.8 years. A somewhat higher proportion of subjects assigned to epoetin alfa treatment had extensive-stage SCLC at diagnosis (66% versus 59% for placebo group). The mean hemoglobin value at baseline was 12.8 g/dL in the epoetin alfa group compared with 13.0 g/dL in the placebo group.

Table 6: Patient Disposition:

(Study N93-004: Intent-to-Treat Population)			
Reason for Discontinuation, no. (%)	Placebo (N=115)	Epoetin Alfa (N=109)	Total (N=224)
Completed planned course of chemotherapy	47 (41%)	49 (45%)	96 (43%)
Disease progression	12 (10%)	13 (12%)	25 (11%)
Adverse event	32 (28%)	23 (21%)	55 (25%)
Subject choice	12 (10%)	12 (11%)	24 (11%)
Protocol violation ^a	1 (1%)	1 (1%)	2 (1%)
Other ^b	10 (9%)	11 (10%)	21 (9%)
Missing information	1 (1%) ^c	--	1 (<1%)

^a Includes subject not receiving cisplatin (epoetin alfa group) and subject for whom blind was broken (placebo group); See Section 4.5.

^b Other reasons for discontinuation included changes to chemotherapeutic regimen (3 epoetin alfa, 3 placebo subjects), toxicity from chemotherapy (2 epoetin alfa, 1 placebo subject), investigator request (1 epoetin alfa, 2 placebo subjects), stable disease with lack of improvement (2 epoetin alfa, 3 placebo subjects), treatment with prohibited concomitant medication (1 epoetin alfa subject), lack of IV access (1 epoetin alfa subject), change in insurance plans (1 epoetin alfa subject), and completed study protocol after 3 cycles of chemotherapy (1 placebo subject).

^c Information on study treatment completion/discontinuation was missing for Subject 1703 who received 2 cycles of chemotherapy and 35 doses of study medication.

J&J PRD's Efficacy Results: This study demonstrated that the overall tumor response rate to chemotherapy among subjects with SCLC treated with 150 IU/kg/t.i.w. epoetin alfa is not lower than that seen in subjects receiving placebo (see Table below). Evaluation of the primary efficacy variable indicated that the percentage of subjects exhibiting a complete or partial tumor response after 3 cycles of cisplatin/etoposide chemotherapy was numerically greater in the epoetin alfa treatment group (72%) than in the placebo group (67%). The 95% confidence intervals on the difference in the primary efficacy endpoint between the treatment groups did not

contain the prespecified limit of -15%, permitting the conclusion that the overall tumor response rate in the epoetin alfa group was not lower than that seen in the placebo group. Among those with extensive-stage SCLC, the overall tumor response rate was 74% in the epoetin alfa treatment group compared with 60% in the placebo group. Among those with limited-stage disease at diagnosis, the overall tumor response rate in the 2 treatment groups was 70% and 77%, respectively. The following table shows the overall tumor response rate for the total population and as function of disease stage at diagnosis.

Table 7: Overall Tumor Response:

	Placebo	Epoetin Alfa
Total ITT Population		
N	115	109
Overall Tumor Response Rate (95% CI)	67% (58% to 76%)	72% (64% to 81%)
Difference (Epoetin alfa minus Placebo) (95% CI)	6% (-6% to 18%)	
Extensive Stage SCLC at Diagnosis		
N	68	72
Overall Tumor Response Rate (95% CI)	60% (49% to 72%)	74% (63% to 84%)
Difference (Epoetin alfa minus Placebo) (95% CI)	13% (-2% to 29%)	
Limited-Stage SCLC at Diagnosis		
N	47	37
Overall Tumor Response Rate (95% CI)	77% (64% to 89%)	70% (56% to 85%)
Difference (Epoetin alfa minus Placebo) (95% CI)	-6% (-25% to 13%)	

Subjects in this study received between 1 and 12 cycles of chemotherapy; the median number of chemotherapy cycles received was 4 for both treatment groups. Subjects in the 2 treatment groups also received similar doses of cisplatin and etoposide; for both groups the median dose of cisplatin ranged from 90 to 100 mg/m² across the first 3 cycles, while the median dose of cisplatin was 300 mg/m². The tumor response rates after all chemotherapy cycles were similar for the epoetin alfa (60%) and placebo (56%) treatment groups (observed difference of 4%; 95% CI of -9% to 17%).

A total of 201 of the 224 subjects were known to have died prior to the end of the 3-year follow-up period. The overall mortality rate, however, was comparable in the epoetin alfa (92%) and placebo groups (88%) as was median survival, which was reached in 10.5 months among epoetin alfa-treated subjects and in 10.4 months among placebo-treated subjects. Baseline hemoglobin levels were maintained in the epoetin alfa group during the first 22 weeks of the study, with weekly hemoglobin levels ranging from 11.3 to 12.7 g/dL. By comparison, hemoglobin levels were reduced in the placebo group during the period subjects were on chemotherapy, with mean levels generally averaging between 10 and 11 g/dL. Fewer subjects in the epoetin alfa group required a RBC transfusion during the study treatment phase (24%) compared with the placebo group (37%). The percentage of subjects with a ECOG performance status score of 0 or 1 at the baseline and final visit was 72% and 45%, respectively, in the placebo group compared with 67% and 53%, respectively, in the epoetin alfa group.

Safety: All subjects in this study reported at least 1 treatment-emergent adverse event during the double-blind treatment phase. Overall, treatment with epoetin alfa did not result in adverse events that were unexpected for a population undergoing chemotherapy with a etoposide/cisplatin regimen for SCLC. Across both treatment groups, the most frequently reported adverse events were nausea, vomiting, alopecia, constipation, fatigue, granulocytopenia, anorexia, asthenia, diarrhea, fever, and dyspnea. During the double-blind treatment phase, thrombotic vascular adverse events occurred in a similar proportion of epoetin alfa- (22%) and placebo-treated subjects (23%). The percentage of subjects who died was similar in the epoetin alfa group (92%) and placebo group (88%). The most frequent cause of death reported in

subjects who died was disease progression (91 [91%] of 100, epoetin alfa; 85 [84%] of 101, placebo). Approximately three-quarters of subjects in the placebo (74%) and epoetin alfa (77%) treatment groups had a serious adverse event. Most of the serious adverse events were related to the subject's underlying malignancy or to the chemotherapeutic regimen, and virtually all were considered by the investigator to be of doubtful relationship or unrelated to study treatment. The percentage of subjects who discontinued study treatment due to an adverse event(s) was 21% in the epoetin alfa group and 28% in the placebo group. For the majority of subjects in both treatment groups, the adverse events that resulted in discontinuation were judged by the investigator of doubtful relationship or unrelated to study medication. There were no clinically meaningful differences between the 2 treatment groups in blood pressure measurements, and the percentage of subjects who had uncontrolled hypertension (i.e., diastolic blood pressure >100 mmHg) while on-study treatment was similar in the epoetin alfa and placebo groups.

Review Comments regarding Amgen's proposal:

Amgen's [REDACTED] (b) (4) study was designed with a sample size of 400 patients to detect a non-inferiority margin of 15%. Since the study was terminated prematurely with enrollment of only 224 subjects, the non-inferiority inference is not valid.

The information of the study was included in a previous version of the label, when there were no safety signals from any other studies and this was the only study where any results regarding tumor outcomes were available. [REDACTED] (b) (4)

Additional Review Comments:

Since this study had a hemoglobin entry criteria well beyond the labeled indication, this study is not useful in determining the optimal hemoglobin level for initiation of ESA therapy or the hemoglobin level (<12 g/dL) at which to withhold or discontinue epoetin alfa.

Review of other studies:

Amgen supported the label changes regarding the hemoglobin level at which ESA's should be initiated and the level at which ESA's should be suspended based on subject level combined analysis of darbepoetin studies (please see Dr. Fan's review STN 103951.5173) and also included similar analyses using epoetin alfa studies. It should be noted that in the annotated label that Amgen submitted in this application, only darbepoetin studies were referred to. However, in the summary of clinical safety (section 2.7.4), Amgen included tables and figures from subject level combined analysis from 11 epoetin alfa studies. Two of these studies are already discussed above. A brief review of these other studies included in Amgen's subject level combined analysis is provided below. Overall it fortifies the view that these heterogeneous studies can not be combined to derive a definite conclusion on the safety of ESAs at a particular hemoglobin level. It should be noted that in absence of a stratification by hemoglobin level at study entry, all analyses is exploratory and do not support a conclusion for a 'safe' starting hemoglobin.

(3) Study J89-40:

Title of Study: The Effect of Subcutaneous r-HuEPO in Patients With Chronic Lymphocytic Leukemia.

Studied Period (years): September 14, 1990 - January 31, 1994

Objectives: The objective of this study was to determine the effect of subcutaneous recombinant human erythropoietin (epoetin alfa; r-HuEPO) on hematocrit and quality of life in anemic, chronic lymphocytic leukemia (CLL) patients.

Methodology: This was a multicenter study that consisted of two treatment phases: a 12-week, randomized, double-blind, placebo-controlled phase, followed by a 12-week, open-label phase. Patients with CLL whose pre-study hematocrit was <32% received either r-HuEPO 150 IU/kg or placebo three times weekly by subcutaneous injection. Patients were randomized to treatment groups in a 2:1 fashion (i.e., two patients received r-HuEPO for every one patient who received placebo). Patients who completed the double-blind phase of the study were eligible to enter the open-label phase, during which all patients received r-HuEPO at a dose titrated to maintain a hematocrit between the target of 38% to 40%. Patients were allowed to receive concomitant chemotherapy and/or prednisone for their underlying CLL; the protocol allowed for changes in their chemotherapy regimen if medically mandatory.

Diagnosis and Main Criteria for Inclusion: Male or female patients with CLL and a history of documented lymphocytosis were eligible to participate in this study. Patients could have received no treatment, prednisone, or a single agent or combination chemotherapy regimen for their CLL, were to be at least 18 years old, have a performance score of 0, 1, 2, or 3, and have a life expectancy of six months or greater. All female patients must have been postmenopausal for at least one year, surgically sterile, or practicing an acceptable method of birth control and have a negative serum pregnancy test prior to study entry. Patients must have been clinically stable with hematocrit <32%, corrected reticulocyte count <3%, platelets >25,000 cells/mm³, and creatinine <2.0 mg/mL. In addition, patients were to have no occult blood in the stool, have a negative direct Coombs test or be Coombs positive with no evidence of active hemolysis, and have been able to administer self-injections.

Efficacy: The primary determination of efficacy was the effect of r-HuEPO on the change in hematocrit from baseline to the completion of the double-blind phase or to early withdrawal. Secondary evaluations included transfusion requirements (cumulative transfusion rate, the proportion of patients becoming transfusion-independent, and the proportion of patients transfused on-study), the proportion of patients achieving a hematocrit of 38% to 40% (correctors) at any time during the study (in the absence of recent transfusion), the proportion of patients achieving a six percentage point increase in hematocrit (responders) at any time during the study (in the absence of recent transfusion), and the change in quality-of-life parameters. The SF-36, two subscales from the SIP (Cognitive Function. Sleep and Rest), and the CLAS

were administered on Day 1 of treatment ("baseline"), at the end of week 6 ("week 6") and at the end of week 12 or early termination for quality of life assessments.

Safety: Safety determinations were based on the incidence and severity of adverse events, deaths, discontinuations, and changes in clinical laboratory tests and vital signs from baseline to final value.

Statistical Methods: The change in hematocrit from baseline to endpoint was analyzed using a linear model with treatment group as the main effect and with the following covariables: stage of disease, baseline chemotherapy usage, baseline splenomegaly, baseline transfusion status, baseline neutrophil count, baseline platelet count, and endogenous erythropoietin (EPO) level. Interactions were studied graphically. Cumulative 12-week on-study transfusion rates were compared between groups by using the two-sample t-test; Fisher's exact test was used to compare the proportion of patients transfused in each treatment group. In addition, a linear model analysis of the cumulative transfusion rates was performed. The proportion of patients who became transfusion-independent was determined (i.e., patients with at least one transfusion during the three months prior to study entry but with no transfusions during Months 2 and 3 of the study). The proportion of patients becoming transfusion-independent was compared between treatment groups using Fisher's exact test. The 0.05 level of significance was used for all statistical tests, except for tests of interaction in the linear models, where the 0.10 level of significance was used.

Efficacy Results: The results only from 221 patients accrued and randomized in North America were provided; those in North America received Epogen/Procrit, while those at other sites received Eprex (epoetin alfa, Ortho Biotech). The least squares mean estimates of change in hematocrit were significantly different between treatment groups overall and within the subgroups determined by baseline chemotherapy. In each case, the improvement in hematocrit was greater in the r-HuEPO group than in the placebo group. Treatment mean differences were significant at the level of cytotoxic chemotherapy without fludarabine subgroup (change from baseline: 7.4% r-HuEPO, 0.7% placebo) and at the level of no cytotoxic chemotherapy (5.8% r-HuEPO, 1.7% placebo). There were no statistically significant differences between treatment groups in transfusion requirements or in quality-of-life outcomes.

Table 8: Transfusion Rates ITT

Population:

Population	Baseline ^a			Cumulative ^b		
	r-HuEPO	Placebo	p-value ^c	r-HuEPO	Placebo	p-value ^c
Overall						
N	142	79		142	79	
Mean	3.0	3.1	0.904	5.8	8.0	0.305
SD	5.1	4.4		10.7	17.5	
Baseline Transfusion Status=Yes						
N	63	45		63	45	
Mean	6.7	5.4	0.203	9.6	11.0	0.696
SD	5.9	4.6		11.0	22.2	
Baseline Transfusion Status=No						
N				79	34	
Mean	NA			2.7	4.0	0.396
SD				9.5	6.5	

^a Baseline transfusion rate is number of units transfused over the three months prior to the first day of study medication (i.e., Day -83 through Day 0).

^b Cumulative transfusion rate = $\frac{84 \times (\text{units of packed RBCs} + \text{units of whole blood})}{\text{Number of on-study days}}$

^c Comparison of treatment groups using t-test.

NA = Not Applicable

There were significant differences between treatment groups in the proportion of responders and in the proportion of correctors. Sixty-seven (47.2%) patients in the r-HuEPO group and 13 (16.5%) patients in the placebo group achieved at least a six percentage point increase in hematocrit (responders) at some point during the study, unrelated to transfusions ($p < 0.0001$). Forty-six (32.4%) patients in the r-HuEPO group reached the target hematocrit of 38% (correctors), unrelated to transfusions, compared to six (7.6%) patients in the placebo group ($p < 0.0001$).

It should be noted that 43% of patients in the r-HuEPO group and 38% of patients in the placebo group received no cytotoxic chemotherapy.

Safety Results: All 221 patients enrolled in North America were evaluated for safety. One hundred twenty-three (87%) patients in the r-HuEPO treatment group and 70 (89%) patients in the placebo treatment group reported at least one adverse event during the double-blind phase of the study, including events considered by the investigator as related or unrelated to administration of the study drug. The most frequently reported adverse events were fever in the r-HuEPO group (23%) and the placebo group (25%), followed by diarrhea and fatigue (18% each) in the r-HuEPO group, and upper respiratory infection (19%) and diarrhea and nausea (18% each) in the placebo group. The majority of adverse events were assessed as mild or moderate in severity. Fifteen patients died during the double-blind phase of the study: 11 (8%) in the r-HuEPO group and 4 (5%) in the placebo group. The majority of deaths were related to CLL disease progression. Sixteen patients were discontinued due to an adverse event: 12 (8%) in the r-HuEPO group and 4 (5%) in the placebo group. Of these 16 patients, seven patients died due to these adverse events (six in the r-HuEPO group, one in the placebo group.) Most of the adverse

events that caused discontinuation occurred in the cardiovascular and respiratory systems. A total of 47 patients experienced serious adverse events: 28 (20%) in the r-HuEPO group and 19 (24%) in the placebo group. There were no clinically significant treatment-emergent mean changes from baseline to final value (value measured at completion of the double-blind phase or early discontinuation) for any laboratory analyte.

Review Comments for Study:

There were no differences between treatment groups in transfusion requirements, which is the parameter used to determine clinical benefit of ESAs. Notwithstanding the caveats regarding the instruments used in quality of life measurements, there were no statistically significant differences in the quality-of-life outcomes for any variable between the treatment group and placebo group.

(4) CC2574-P-174

STUDY DESIGN

Study Title: "The effect of subcutaneous epoetin alfa (RWJ 22512/EPREX) in patients with chronic lymphocytic leukemia (Protocol CC2574-P-174)"

Dates of Study: October 23, 1991 to August 10, 1994

Date of Clinical Study report: 12 March 1999

Study Centers: Praha, Copenhagen, Paris, Leicester, Athens, Budapest, Bologna, Palermo, Roma, Catanzaro, Ferrara, Poznan, Warszawa, Barcelona.

Number of patients: 45 (33 Epoetin alfa and 12 placebo)

Description of Trial: This European trial was split off from protocol J89-040 by protocol amendment when the proposed sample size of 216 patients for J89-040 was fully accrued in the US and Canada. Protocol CC2574-P-174 is a Phase II, double blind, multicenter (14 sites), randomized (2:1), placebo-controlled trial. The study was stopped after 3 years at which time 45 patients (out of a planned 216) were enrolled, 33 in the epoetin group and 12 in the placebo group. Subjects received either epoetin alfa (150IU/kg with the option to increase or decrease the dose by 50 IU/kg depending on response) or placebo three times per week x 12 weeks, or until the Hematocrit (Hct) reached 38-40%. During the 12 week open label follow-up phase, a patient's response was to be evaluated during the double-blind phase of the study and treated as follows: if the hematocrit was not 38-40%, epoetin alfa was to be given in incremental or decremental doses of 50 IU/kg higher/lower than the dose in the double-blind phase to maintain the hematocrit between 38-40%. The maximum dose in this phase was 300 IU/kg 3x/week. An optional maintenance phase added by protocol amendment was permitted for patients who had responded to the drug (i.e., hemoglobin > 11.5 g/dL) and completed the open-label phase. During this phase, the starting dose was to be the same as the final dose given in the open-label phase, with a target hematocrit of 35% and titration permitted in 25-50IU/kg increments. Dosing was

stopped during this phase for a hematocrit of 45%. During all phases of the study, patients were to receive folate 1 mg/day and supplemental iron could be given at the investigators' discretion.

Study Population: Patients with CLL (defined by standard clinical criteria and staged using the Rai classification system) with anemia, defined as a Hct < 32% on two occasions at least two weeks apart in the month prior to study entry. Patients were to have been on a stable regimen which could include no treatment, prednisone, a single agent (fludarabine or chlorambucil) with or without prednisone, or a combination regimen consisting of CHOP or CVP for at least one month prior to enrollment with no anticipated change in treatment for three months. In practice, patients were permitted to continue if their regimen changed. Patients were excluded for significant pulmonary, cardiovascular, endocrine, neurological, gastrointestinal, or genitourinary system disease or dysfunction not attributable to their malignancy. Uncontrolled hypertension (HTN), a history of seizures, current untreated iron, folate, or B12 deficiency, and androgen therapy within 2 months of study entry were also excluded. In addition, patients were excluded who had received a transfusion (# units not specified) within 1 week of study medication.

Study Objectives and Endpoints: The objective of the study was to determine the effect of subcutaneous epoetin alfa on hematocrit and QOL in anemic patients with CLL. The primary efficacy variable was hematocrit level. Secondary variables were hemoglobin level, transfusion rates, hematocrit (responders and correctors), quality of life questionnaire, and subject performance scores.

Efficacy Assessments: An erythropoietin level, an erythropoietin antibody level, CBC and reticulocyte count were obtained on Day 1 prior to initial dosing. CBC and reticulocyte counts were repeated weekly. Bone marrow aspirates and biopsies were obtained at selected sites within 2 weeks of study entry and repeated at the completion of the double-blind phase of the study within 48 hours of the last dose of study drug. QOL surveys were to be completed on day 1 prior to dosing, after weeks 6 and 12 of treatment, or early termination. The investigator was also to rate the effect of the study medication and determine a performance score after weeks 6 and 12.

QOL Instruments: (1) Medical Outcomes Study Short Form 36 (SF-36) scales for Physical Function, Role-Physical, Pain, General Health, Vitality, Social Function, Role-Emotional, and Mental Health. (2) Cognitive function, Sleep and Rest subscales of the Sickness Impact Profile (SIP). (3) Cancer Linear Analogue Scales (CLAS) for Energy, Activities, and Overall QOL.

Safety Assessments: Adverse event reporting, vital signs, and clinical laboratory data were used to assess safety during the study.

Statistical Analysis Plan: The statistical analysis plan described in the protocol was designed and powered for a total of 216 patients with a 2:1 randomization. Decrease in the sample size reduced the statistical power of the study from 80% to 27%. RW Johnson PRI noted that no distinction was made between the efficacy and intent-to-treat populations for the purposes of analyses in the study because all randomized subjects received at least 15 days of therapy. In addition, due to the small number of patients recruited, the planned analyses were simplified and

restricted mainly to the double-blind phase. All analyses planned with a multivariate model correcting for potential confounding variables were replaced by simple univariate analyses. Open-label phase data were integrated into the by-patient listings of the raw data. Maintenance phase data (6 patients) were not reported.

Patient demographics and tumor characteristics: A total of 45 patients were randomized to the study, 33 in the epoetin cohort and 12 in the placebo cohort.

Demographic characteristics were similar between treatment cohorts. The mean age was 64.7 years. All patients were caucasian, and fifteen subjects (33%) were male. In the epoetin cohort, 13 patients (39%) had stage IV disease at baseline, while 9 patients (75%) had stage IV disease at baseline in the placebo cohort. In the epoetin cohort, 24 patients (73%) had received chemotherapy prior to enrollment, while 11 patients (92%) in the placebo cohort had received chemotherapy prior to enrollment. The mean duration from diagnosis for the epoetin cohort was 44.5 months, and for the placebo cohort, 64.2 months.

The following table shows the chemotherapy regimens used. Note that overall 40 % of subjects did not receive chemotherapy.

Table 9: Chemotherapy regimens

	r-HuEPO (N= 33)	Placebo (N= 12)	Overall (N= 45)
Platelet Nadir [10⁹/L]			
0 < - <20	2 (6.1%)	3 (25.0%)	5 (11.1%)
20 - <50	9 (27.3%)	3 (25.0%)	12 (26.7%)
≥50	22 (66.7%)	6 (50.0%)	28 (62.2%)
Absolute Neutrophil Count [10⁶/L]			
0 < - <500	32 (97.0%)	12 (100%)	44 (97.8%)
500 - <1000	1 (3.0%)	0 (0.0%)	1 (2.2%)
Chemotherapy Used on Study			
No	14 (42.4%)	4 (33.3%)	18 (40.0%)
Yes	19 (57.6%)	8 (66.7%)	27 (60.0%)
Chemotherapy Combinations Used on Study			
(nothing)	14 (42.4%)	4 (33.3%)	18 (40.0%)
ADRIPLASTIN/ CYCLOPHOSPHAMIDE/ DECADRON/ ENDOXAN/ PREDNISONE/ VINBLASTINE	0 (0.0%)	1 (8.3%)	1 (2.2%)
BLEOMYCIN/ CYCLOPHOSPHAMIDE/ VINCRISTINE	1 (3.0%)	0 (0.0%)	1 (2.2%)
CHLORAMBUCIL	5 (15.2%)	2 (16.7%)	7 (15.6%)
CHLORAMBUCIL/ DEFLAZACORT	1 (3.0%)	0 (0.0%)	1 (2.2%)
CHLORAMBUCIL/ INTERFERON	0 (0.0%)	1 (8.3%)	1 (2.2%)
CHLORAMBUCIL/ LEUKERAN/ PREDNISONE	1 (3.0%)	0 (0.0%)	1 (2.2%)
CHLORAMBUCIL/ METHYLPREDNISOLONE	2 (6.1%)	0 (0.0%)	2 (4.4%)
CHLORAMBUCIL/ PREDNISONE	5 (15.2%)	1 (8.3%)	6 (13.3%)
CYCLOPHOSPHAMIDE DECADRON/ NITROGEN MUSTARD/ PREDNISONE/ PROCARBAZINE/ VINBLASTINE	1 (3.0%)	2 (16.7%)	3 (6.7%)
ENDOXAN/ METHYLPREDNISOLONE	1 (3.0%)	1 (8.3%)	2 (4.4%)
FLUTARABINE	1 (3.0%)	0 (0.0%)	1 (2.2%)

Conduct of Trial: The table below, excerpted from the CSR, depicts the disposition of patients enrolled in the double-blind phase of study CC2574-P-174. Other study conduct was not discussed in the clinical study report (CSR).

Table 10: Disposition of Patients in the Double-Blind Phase

	r-HuEPO (N= 33)	Placebo (N= 12)	Overall (N= 45)
Patients Entered			
N	33 (100%)	12 (100%)	45 (100%)
Disposition			
DB-Phase Discontinued, Target Hct not Reached	3 (9.1%)	0 (0.0%)	3 (6.7%)
12 Weeks DB-Phase Completed, Target Hct not Reached	17 (51.5%)	11 (91.7%)	28 (62.2%)
Target Hct (38%, not Tx-Related) Reached in DB-Phase	13 (39.4%)	1 (8.3%)	14 (31.1%)
Reason for Premature Discontinuation *			
missing	1 (33.3%)		1 (33.3%)
Adverse Experience	2 (66.7%)		2 (66.7%)

*) Patients # 3201 3501 9501

Efficacy Results: For change in hematocrit, a primary efficacy variable in the study, the mean change from baseline was 5.4% in the epoetin group and 3.3% in the placebo group. The difference between the treatment groups for change from baseline in hematocrit level was not significant (p = 0.274). The table below, excerpted from the CSR, depicts the results of the primary efficacy analysis for change in hematocrit on study CC2574-P-174.

Table 11: Change in Hct % from Baseline to End of Double-blind Phase (ITT)

Period	Statistic	r-HuEPO (N=33)	Placebo (N=12)	P-Value (t-Test)
Pre-Study	N	33	12	
	Mean	27.5	26.0	
	Median	28.0	25.4	
	Std.Dev.	4.25	2.99	
	Minimum	15.0	22.5	
	Maximum	34.3	32.4	
End of Double Blind Phase	N	33	12	
	Mean	32.9	29.4	
	Median	33.3	29.7	
	Std.Dev.	6.43	3.93	
	Minimum	17.1	22.0	
	Maximum	43.0	35.9	
Change from Baseline to End of Double Blind Phase	N	33	12	
	Mean	5.4	3.3	0.274
	Median	7.3	3.6	
	Std.Dev.	5.77	5.05	
	Minimum	-7.7	-4.0	
	Maximum	12.4	11.2	

The proportion of patients transfused is shown below:

Table 12: Proportion of Patients Transfused

Transfused Pre-Study	Transfused On-Study	r-HuEPO (N= 33)		Placebo (N= 12)	
		N	(%)	N	(%)
Yes	Yes	7	(21.2)	1	(8.3)
	No	4	(12.1)	0	(0.0)
No	Yes	2	(6.1)	4	(33.3)
	No	20	(60.5)	7	(58.3)

Cochran-Mantel Haenszel Test Stratified by Transfusion Status at Baseline:
 Chi-Square: 4.041
 df: 1
 P-Value: 0.044

For the QOL data, 11/13 patients' mean quality-of-life change scale scores were increased at Week 6 within the epoetin group, while none of the quality-of-life scale scores increased significantly within the placebo group. There were no significant differences in QOL between the two treatment groups at Week 12.

Safety: The adverse events incidence rates were similar in the two groups. One 71 year old subject with history of ischemic heart disease assigned to Epoetin alfa died of congestive heart failure. One subject discontinued due to pulmonary edema.

Review Conclusions: This was a small study in which very few patients needed transfusions and therefore it would be difficult to draw conclusions regarding the level at which ESA should be initiated. With due caveats of the instruments, and statistical analysis that used mean scores, a statistical improvement in QOL was not shown.

(5) EPO-INT-1

Amgen provided an incomplete study report. The entire study report submitted contained first 39 pages of the 1812 pages cited in the table of contents page. As per Amgen, the study was conducted the study outside the US and was never submitted to a health authority. Hence they were not able to locate the case report forms or appendices noted to in the clinical study report.

Study Title: "Randomized Double-blind Study On The Effect of Epoetin Alfa In Subjects With Ovarian Cancer Receiving Cyclic Platinum Based Chemotherapy Regimens"

Study initiation date: April 2, 1993

Study completion date: February 13, 1997

Patient Population: Ovarian cancer receiving cisplatinum

Randomization: 2:1 to 300 IU/kg SQ epoetin alfa (Eprex) or placebo, or 150 IU/kg SQ epoetin alfa or placebo three times per week.

Study sites: The study was conducted in 49 sites in 17 European countries (Czechoslovakia, Italy, Poland, Spain, United Kingdom, Austria, Germany, Hungary, France, Bulgaria, Greece, the Netherlands, Portugal, Israel, Sweden, Yugoslavia, and Finland), enrolled 246 subjects (240 planned).

Study Entry criteria: Baseline hemoglobin prior to chemotherapy < 11 g/dL, or whose hemoglobin had decreased from baseline ≥ 1.5 g/dL when baseline prior to chemotherapy was <14 g/dL, or ≥ 2 g/dL when baseline prior to chemotherapy was ≥ 14 g/dL.

Dose Adjustment: For patients in the 150 IU/kg epoetin alfa group, reticulocyte counts were compared after four weeks of therapy to baseline values. If the reticulocyte count increased \geq

40,000/ μ L above baseline, the dose of study drug remained at 150 IU/kg. If the increase was <40,000/ μ L, the dose was adjusted to 300 IU/kg. However, if the hemoglobin concentration rose ≥ 1 g/dL after four weeks of therapy with 150 IU/kg epoetin alfa, the dose was maintained regardless of the magnitude of change in reticulocyte count.

If the hemoglobin level for any subject in any group exceeded 14 g/dL, study drug was withheld until the hemoglobin concentration fell below 12.5 g/dL at which time study drug was restarted at a dose approximately 25% below that previously administered. The dose of study drug was also reduced by approximately 25% if the hemoglobin concentration increased at a rate ≥ 2 g/dL per month. Study drug administration continued for one month after completion of the last cycle of chemotherapy.

Transfusions were permitted as needed during the trial; however, every an effort was made not to transfuse subjects with hemoglobin concentrations >8 g/dL.

Study Objectives and Endpoints: The primary study objective was the comparison of two epoetin alfa treatment regimens and placebo for anemia prevention and transfusion dependence in subjects with ovarian cancer being treated with cyclic platinum-based chemotherapy. The primary efficacy endpoint was the proportion of patients in the intent-to-treat and efficacy populations transfused during month 2 and 3 on study stratified by baseline transfusion status and overall. Secondary endpoints discussed in the CSR include proportion of patients transfused having hemoglobin (hgb) < 8 g/dL during month 2 or 3, time to first transfusion, cumulative transfusion rate, hemoglobin and hematocrit, performance score and physician's global assessment, quality of life, patients who doubled their dose, type of chemotherapy, and iron supplementation. It should be noted that neither the protocol nor statistical analysis plan (SAP) were provided with this submission. Therefore the analysis of pre-specified endpoints, and appropriateness of statistical tests, and alfa spending as planned in the protocol and SAP cannot be commented upon.

Patient demographics and tumor characteristics: A total of 246 patients were randomized to the study, including 80 patients who received epoetin alfa 300 IU/kg, 85 who received 150 IU/kg, and 81 who received placebo (38 received 300 IU/kg placebo and 43 received 150 IU/kg placebo). The treatment groups were comparable with respect to demographic and baseline characteristics. Mean baseline hemoglobin levels were the same for the three groups (9.9 g/dL), and neutrophil counts were comparable (63.5% overall). The mean serum erythropoietin level at baseline was higher in the 300 IU/kg epoetin alfa group (122 mU/mL) compared with levels in both the 150 IU/kg epoetin alfa and placebo groups (79 mU/mL and 78 mU/mL, respectively). Overall, 21% of the 300 IU/kg epoetin alfa-treated group, 15% of the 150 IU/kg epoetin alfa-treated group, and 17% of the placebo-treated group were transfusion-dependent at baseline. Patients received a mean of 0.6 units of blood in the previous three months; although the prestudy transfusion rate for the epoetin alfa 150 IU/kg group (0.4 units) was slightly lower than for the epoetin alfa 300 IU/kg group (0.7 units) and the placebo group (0.6 units), the difference was not clinically relevant. In addition, for those subjects transfused, the prestudy transfusion

rate was 2.5 units for the epoetin alfa 150 IU/kg group, 3.3 units for the epoetin alfa 300 IU/kg group, and 3.6 units for the placebo group.

Efficacy Results: For the primary efficacy variable, the proportion of subjects transfused during months 2 and 3, there were no statistically significant differences between the treatment groups for either the efficacy analysis population or the intent-to-treat population. The table below, excerpted from the CSR, depicts these results.

Table 13: Proportion of Patients Transfused During Months 2 or 3 by Pre-study Transfusion Dependence (Protocol CC 2574-P-416)

Transfused Prestudy	Transfused During Months 2 or 3	Epoetin Alfa 300 IU/kg N (%)	Epoetin Alfa 150 IU/kg N (%)	Placebo N (%)	p-value ^a
Efficacy Population^b		(N=68)	(N=77)	(N=77)	300 IU/kg vs placebo: p=0.127
Yes	Yes	2 (15.4)	5 (45.5)	6 (42.9)	300 IU/kg vs 150 IU/kg: NA
	No	11 (84.6)	6 (54.5)	8 (57.1)	150 IU/kg vs placebo: NA
No/Unknown	Yes	9 (16.4)	7 (10.6)	8 (12.7)	300 IU/kg vs placebo: p=0.796
	No	46 (83.6)	59 (89.4)	55 (87.3)	300 IU/kg vs 150 IU/kg: NA 150 IU/kg vs placebo: NA
Intent-to-Treat Population^c		(N=80)	(N=85)	(N=81)	300 IU/kg vs placebo: p=0.475
Yes	Yes	6 (35.3)	7 (53.8)	6 (42.9)	300 IU/kg vs 150 IU/kg: NA
	No	11 (64.7)	6 (46.2)	8 (57.1)	150 IU/kg vs placebo: NA
No/Unknown	Yes	17 (27.0)	13 (18.1)	12 (17.9)	300 IU/kg vs placebo: p=0.927
	No	46 (73.0)	59 (81.9)	55 (82.1)	300 IU/kg vs 150 IU/kg: NA 150 IU/kg vs placebo: NA

^a Fisher's exact test, one-sided.

^b Cochran-Mantel Haenszel Test stratified by transfusion status at baseline: chi-square: 0.118 df: 1 p-value (2-sided/2): 300 IU/kg vs placebo: p=0.366; 300 IU/kg vs 150 IU/kg: NA; 150 IU/kg vs placebo: NA.

^c Cochran-Mantel Haenszel Test stratified by transfusion status at baseline: chi-square: 0.741 df: 1 p-value (2-sided/2): 300 IU/kg vs placebo: p=0.195; 300 IU/kg vs 150 IU/kg: NA; 150 IU/kg vs placebo: NA.

Cross-reference: Appendix 2.3: Attachment 13, 14, 15, 16, 17; Appendix 3.6.

Safety Results: The table below depicts Amgen's analysis of treatment-emergent adverse reactions.

Table 14: Incidence of treatment-emergent adverse reactions in $\geq 5\%$ of patients by PT

(Protocol CC 2574-P-416)

Body System Preferred Term	Epoetin Alfa 300 IU/kg (N=80)	Epoetin Alfa 150 IU/kg (N=84)	Placebo (N=80)	Overall (N=244)
	N (%)	N (%)	N (%)	N (%)
Any adverse event	53 (66%)	53 (63%)	51 (64%)	157 (64%)
White cell and RES disorders	27 (34%)	27 (32%)	26 (33%)	80 (33%)
Leukopenia	24 (30%)	21 (25%)	21 (26%)	66 (27%)
Granulocytopenia	8 (10%)	7 (8%)	8 (10%)	23 (9%)
Platelet, bleeding & clotting disorders	26 (33%)	23 (27%)	20 (25%)	69 (28%)
Thrombocytopenia	25 (31%)	22 (26%)	20 (25%)	67 (27%)
Gastrointestinal system disorders	9 (11%)	19 (23%)	16 (20%)	44 (18%)
Vomiting	5 (6%)	10 (12%)	10 (13%)	25 (10%)
Nausea	3 (4%)	5 (6%)	7 (9%)	15 (6%)
Abdominal pain	1 (1%)	2 (2%)	4 (5%)	7 (3%)
Body as a whole-general disorders	17 (21%)	8 (10%)	15 (19%)	40 (16%)
Fever	5 (6%)	2 (2%)	3 (4%)	10 (4%)
Edema	4 (5%)	1 (1%)	0	5 (2%)
Red blood cell disorders	8 (10%)	7 (8%)	7 (9%)	22 (9%)
Anemia	7 (9%)	6 (7%)	5 (6%)	18 (7%)
Skin and appendages disorders	7 (9%)	6 (7%)	7 (9%)	20 (8%)
Alopecia	4 (5%)	3 (4%)	3 (4%)	10 (4%)
Urinary system disorders	6 (8%)	3 (4%)	6 (8%)	15 (6%)
Resistance mechanism disorders	6 (8%)	3 (4%)	5 (6%)	14 (6%)
Respiratory system disorders	6 (8%)	2 (2%)	6 (8%)	14 (6%)
Central & peripheral nervous system disorders	3 (4%)	7 (8%)	3 (4%)	13 (5%)
Headache	1 (1%)	5 (6%)	1 (1%)	7 (3%)
Cardiovascular disorders, general	5 (6%)	3 (4%)	2 (3%)	10 (4%)
Hypertension	5 (6%)	2 (2%)	2 (3%)	9 (4%)
Psychiatric disorders	2 (3%)	2 (2%)	6 (8%)	10 (4%)

Note: RES = reticuloendothelial system.

Table 15: Deaths:

Table 11: Subjects Who Died
 (Protocol CC 2574-P-416)

Subject	Age (yr)	Adverse Event	Day of Onset	Day of Last Dose	Study End Day	Day of Death	Drug Relationship ^a
Subjects Treated With Epoetin Alfa 300 IU/kg							
143	55	Disease progression ^b	NA	41	41	47	NA
278	74	Pancytopenia ^b	11	13	13	14	Unlikely
		Anemia ^b	11	13	13	14	Unlikely
		Right lower lobe pneumonia ^b	11	13	13	14	Unlikely
290	62	Disease progression	NA	31	31	60	NA
Subjects Treated With Epoetin Alfa 150 IU/kg							
256	48	Personal reason ^c	NA	26	27	55	NA
463	60	Atelectasis ^b	14	13	14	14	Unlikely
		Pulmonary edema ^b	14	13	14	14	Unlikely
507	46	Disease progression	NA	66	67	78	NA
Subjects Treated With Placebo							
433	57	Disease progression	NA	62	62	71	NA
511	66	NA ^d	NA	164	211	216	NA

^a According to the investigator.
^b Classified as serious adverse event.
^c Subject wanted no further therapy. Subject died from disease progression.
^d Subject died from disease progression.
 NOTE: yr = year(s); NA = not available.
 Cross-reference: Appendix 3.8.

Table 16: Subjects with thrombovascular events:

Table 12: Subjects Who Had Thrombotic/Vascular Events (Safety Population)
 (Protocol CC 2574-P-416)

Subject	Age	Adverse Event	Onset (Day)	Duration or Outcome	Severity	Drug Relationship
Subjects Treated With Epoetin Alfa 300 IU/kg						
171	50	Thrombophlebitis, deep ^a	21	17 days	Marked	Unlikely
451 ^b	59	Bilateral occipital infarction ^c	65	Persisted	Marked	Unlikely
514	56	Phlebitis	44	Resolved	Moderate	Unlikely
		Pulmonary embolism ^c	84	Resolved	Marked	Unlikely
Subjects Treated With Epoetin Alfa 150 IU/kg						
081	45	Multiple superficial thrombophlebitis	20	NR	Mild	Unlikely
173	73	Thrombophlebitis, deep ^c	8	94 days	Moderate	Possible
452 ^b	73	Cerebrovascular disorder	25	1 day ^d	Marked	Possible
Subjects Treated With Placebo						
203 ^a	51	Phlebitis	80	Persisted	Moderate	Unlikely
257	73	Thrombophlebitis	58	Persisted	Mild	Unlikely

^a Subject withdrew from study because of the adverse event.
^b Subject withdrew from study for reason other than adverse event.
^c Serious adverse event.
^d This event resulted in permanent disability.
 Note: NR = not reported.
 Cross-reference: Appendix 3.8.

Table 17: Discontinuation:

Table 15: Subjects Who Discontinued Due to Adverse Events (Safety Population)
 (Protocol CC 2574-P416)

Subject	Age	Adverse Event	Onset (Day)	Duration	Study End (Day)	Severity	Drug Relationship ^a
Subjects Treated With Epoetin Alfa 300 IU/kg							
278 ^b	74	Anemia ^c	11	4 days	13	Marked	Unlikely
		Pancytopenia ^c	11	4 days	13	Marked	Unlikely
		Right lower lobe pneumonia ^c	11	4 days	13	Marked	Unlikely
329	69	Edema of face and neck	2	1 day	1	Moderate	Possible
		Dyspnea	2	1 day	1	Moderate	Possible
451	59	Bilateral occipital infarction ^c	65	Persisted	78	Marked	Unlikely
Subjects Treated With Epoetin Alfa 150 IU/kg							
452	73	Cerebral vascular disorder	25	1 day	25	Marked	Possible
463 ^b	60	Pulmonary edema ^c	14	1 day	14	Marked	Unlikely
		Atelectasia ^c	14	1 day	14	Marked	Unlikely
Subjects Treated With Placebo							
004	70	Intestinal obstruction ^c	75	5 days	105	Marked	Unlikely
203	51	Phlebitis, lower limb	80	Persisted	87	Moderate	Unlikely
388	62	Allergic reaction (urticaria)	12	4 days	36	Moderate	Probable/likely

^aAccording to the investigator.

^bSubject died.

^cSerious adverse event.

Cross-reference: Appendix 3.2, 3.8.

Review Comments:

This much abbreviated study report shows an absence of treatment benefit based on the transfusion endpoints. QOL measurements were not commented upon in the submitted portion of clinical study report. No inferences can be made from the available information. It underscores why a combined subject level analysis is not appropriate.

(6) EPO-INT-2

Amgen submitted an incomplete study report. Numerous attachments are noted as not available in the table of contents.

Study Title: A Placebo-Controlled Study On The Effect Of Epoetin Alfa In Subjects With Multiple Myeloma Followed By An Open-Label Extension

Study initiation date: February 17, 1994
 Study completion date: October 10, 1996
 Study Report date: June 16, 1998

Description of Trial: Phase 3, multicenter, double-blind, placebo-controlled study followed by an open-label extension in patients with multiple myeloma (MM) at high risk for developing transfusion-dependent anemia. The study was stratified into two groups based on whether or not patients had received at least one blood transfusion in the prior three months and were randomly assigned to receive epoetin alfa (Epo) 150 IU SQ three times per week or placebo for an initial period of 12 weeks, then in a 12 week, open-label extension. RBC transfusions were recommended for hemoglobin (hgb) levels ≤ 8 g/dL or as clinically indicated. The individual responsible for making the decision to transfuse was to be kept blinded to reticulocyte count. The study was conducted in 12 countries, Italy, Poland, Great Britain, Norway, Sweden, Czech Republic, Hungary, Belgium, Israel, Denmark, Spain, and Switzerland.

Study Population: A total of 145 patients (135 were planned) with documented MM (major criteria: plasmacytoma on tissue biopsy; bone marrow plasmacytosis with >30% plasma cells; monoclonal globulin spike on serum electrophoresis > 3.5 g/dL for G peaks or 2.0 g/dL for A peaks and 1.0 g/24 hours of k- or l-chain excretion on urine electrophoresis in the presence of amyloidosis) were randomized on the study. Patients had to be at least six months from the start of non-platinum-containing chemotherapy. Baseline hemoglobin was < 11.0 g/dL and reticulocyte count < 100,000/ μ L. Excluded from the study were patients with evidence of untreated iron, folate, or B12 deficiency, patients who had been treated with androgen therapy within two months of study entry, and patients who had received a transfusion within 7 days of study entry.

Study Objectives and Endpoints: The study objective was to reduce or prevent transfusions or anemia in patients with MM and to investigate quality of life (QOL). The primary endpoint was proportion of patients transfused during months 2 and 3 in the intent-to-treat population stratified by pre-study transfusion history. Secondary endpoints included transfusions (overall, time to first transfusion, proportion of patients becoming transfusion independent, and cumulative transfusion rate), change in hemoglobin, hematocrit, and reticulocyte count, change in serum erythropoietin level, response, performance scores, physician's global assessments.

Efficacy Assessments: Weekly hemoglobin measurements and RBC transfusions were used. QOL data was collected

Safety Assessments: Safety evaluations included assessments of adverse events, clinical laboratory tests, vital signs, and physical examinations. Serum and urine M-protein levels were compared for changes in underlying disease.

Patient demographics and tumor characteristics

Demographic and baseline characteristics were generally comparable between treatment groups (Tables 2 and 3). The majority of subjects were enrolled in Italy, Poland, and Great Britain. The mean age was 64.9 years. Slightly more subjects were female (55.2%). The disease stage was also similar between groups, the mean baseline hemoglobin was 9.3 g/dL in the epoetin alfa-treated group and 9.6 g/dL in the placebo-treated group, and the mean baseline percent neutrophil count was 61.1% for epoetin alfa-treated subjects and 61.9% for placebo-treated subjects.

Efficacy Results: The table below, excerpted from the CSR, summarizes the primary efficacy results for the study. The difference in the proportion of patients transfused during months 2 and 3 between treatment groups for both the intent-to-treat and efficacy populations were statistically significant.

For secondary endpoints, there were statistically significant increases in hemoglobin and hematocrit in the epo treated group. Hemoglobin and hematocrit corrected by means of 1.8 g/dL and 6.0% respectively.

Table 18 Patients Transfused Months 2 or 3 By Baseline Transfusion History

Transfused Prestudy	Transfused		150 IU/kg		Placebo		p-Value ^a
	During Months 2 or 3		N	(%)	N	(%)	
Efficacy Population			(N=66)		(N=66)		0.028
Yes	Yes		12	(52.2)	16	(72.7)	
	No		11	(47.8)	6	(27.3)	
No	Yes		4	(9.3)	10	(22.7)	
	No		39	(90.7)	34	(77.3)	
Intent-to-Treat Population			(N=69)		(N=76)		0.006
Yes	Yes		14	(56.0)	22	(78.6)	
	No		11	(44.0)	6	(21.4)	
No	Yes		5	(11.4)	14	(29.2)	
	No		39	(88.6)	34	(70.8)	

^a Cochran-Mantel Haenszel test, comparing the proportions of subjects transfused stratified by prestudy transfusion dependence.

It is not clear from the CSR, how many subjects received chemotherapy during the study, since the appendix containing that information is not provided (attachment 8 of Appendix 3.2 as per CSR).

Based on results from Nottingham Health Profile and Cancer Linear Analog Scales, no significant differences were observed between treatment groups. QOL was also measured by performance status. Fewer epoetin alfa treated subjects had an increase in ECOG performance status of 2 points than placebo (7.6%)

Safety: Treatment-emergent adverse events were similar among treatment groups. Fever, leukopenia, and pain were the most frequently reported adverse events. Similar proportions of subjects (2.9% epoetin alfa-treated and 3.9% placebo-treated) discontinued treatment due to one or more adverse events. More placebo-treated subjects than epoetin alfa-treated subjects died (seven vs. one, respectively) and more placebo-treated subjects than epoetin alfa-treated subjects discontinued treatment due to disease progression (six vs. none, respectively) despite similar multiple myeloma disease staging at baseline and at the end of the study. Serious adverse events were in general similarly distributed both across body systems and between treatment groups.

Review Comments on the study as it relates to determining the level of hemoglobin at which to initiate ESA:

The following table is generated from the data using FDA statistical review:

Table 19 : Proportion of Patients transfused by baseline hemoglobin category:

Study Arm (No. of patients)	Baseline Hb < 9 g/dL	Baseline Hb ≥ 9 g/dL	Baseline Hb <10 g/dL	Baseline Hb ≥ 10 g/dL	Baseline Hb <11 g/dL	Baseline Hb ≥ 11 g/dL
ESA number transfused/ number in group	10/24 (42%)	6/45 (14%)	15/47 (32%)	1/22 (5%)	16/47 (34%)	0/22
Placebo number transfused/ number in group	10/17 (59%)	18/59 (31%)	22/46 (48%)	6/30 (20%)	27/46 (59%)	1/30 (3%)
Total transfused/total Number of pts	20/41	24/104	37/93	7/52	43/93	1/52

The impact of ESA in reducing transfusion requirement was evident in all baseline hemoglobin level cut-offs as seen in the table above, except Hb > 11 g/dL where only 1 of 52 subjects required a transfusion. It should be noted that based on the information provided in the CSR, it is not possible to assess how many subjects received cytotoxic chemotherapy during the study, which is the indicated population for the use of ESAs.

ECOG performance status, which depends on multiple factors, is not an adequate measure of ESAs impact health related quality of life. Additionally, the study only showed minimal effect on that parameter. Based on results from Nottingham Health Profile and Cancer Linear Analog Scales, no significant differences were observed between treatment groups.

(7) EPO-INT-3

Title of Study: A Placebo Controlled Study on the Effect of r-HuEPO in Patients with Malignancy Receiving Chemotherapy

Studied Period (years): 7 February 1995 through 14 May 1998

Date of Clinical Study Report: 12 March 1999

Study Sites: Denmark, Norway, Iceland and Sweden

Objectives: The purpose of this study was to compare the ability of epoetin alfa and placebo to prevent transfusion, to treat or prevent anemia, and to investigate quality-of-life benefits

associated with the use of epoetin alfa in subjects receiving chemotherapy for selected malignancies.

Methodology: This trial was a 12 week multicenter, double-blind, placebo-controlled study conducted in four countries, followed by an open-label extension. EORTC-QLQ-C30 questionnaire was day 1 and at weeks 4, 8, and 12 of the double blind study phase.

Number of Subjects (planned and analyzed): 201 planned and analyzed

Diagnosis and Main Criteria for Inclusion: Subjects were to be between 18 and 80 years old, with a confirmed diagnosis of one of the following: multiple myeloma, lymphoma, breast cancer, ovarian cancer, small-cell lung cancer, esophagus cancer, or prostate cancer. Chemotherapy was to be currently underway or imminent, and subjects were to have a hemoglobin level <12 g/dL or a hemoglobin decline of 1.5 g/dL during the current cycle of chemotherapy, with a performance score (ECOG) of 0, 1, 2, or 3, (i.e., not completely disabled), and a life expectancy of at least six months.

Starting Dose and dose modifications: Epoetin alfa (Eprex or Erypo) was initiated at 150 IU/kg, s.c., t.i.w.; if, after four weeks of therapy, a subject's hemoglobin had increased by less than 1 g/dL above baseline, the initial dose (150 IU/kg t.i.w.) was to be doubled to 300 IU/kg t.i.w. T.

Primary Efficacy Endpoint: Proportion of patients transfused during months 2 and 3

Secondary Endpoints: Hemoglobin related endpoints and QOL

Efficacy Results:

Table 20: Study Completion Withdrawal Information for the Double Blind Phase:

	Epoetin Alfa (N=136)	Placebo (N=65)	Overall (N=201)
Intent-to-Treat Population*			
Completed	105 (77%)	56 (86%)	161 (80%)
Withdrawn	31 (23%)	9 (14%)	40 (20%)
Adverse Event	15 (11%)	3 (5%)	18 (9%)
Patient's Request	7 (5%)	5 (8%)	12 (6%)
Investigator's Decision	7 (5%)	0 (0%)	7 (3%)
Lost to Follow-up	0 (0%)	0 (0%)	0 (0%)
Other	2 (1%)	1 (2%)	3 (1%)
Efficacy Population	(N=108)	(N=57)	(N=165)
Completed	92 (85%)	52 (91%)	144 (87%)
Withdrawn	16 (15%)	5 (9%)	21 (13%)
Adverse Event	7 (6%)	2 (4%)	9 (5%)
Patient's Request	4 (4%)	3 (5%)	7 (4%)
Investigator's Decision	5 (5%)	0 (0%)	5 (3%)
Lost to Follow-up	0 (0%)	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)	0 (0%)

* All subjects enrolled; identical to safety population except for one subject (79) in the epoetin alfa group who received no study medication and withdrew upon request.

Protocol Deviations: 25 subjects did not receive any chemotherapy during the course of the study (19 subjects in the ESA group and 6 in the placebo group).

The study showed efficacy of epoetin alfa in reducing the number of transfusions and improvement in hemoglobin related endpoints.

Table 21: Proportion of Patients Transfused During Months 2 and 3

Transfused During Months 2 or 3	Epoetin Alfa N (%)	Placebo N (%)	p value ^a
Intent-to-Treat Population (N=136)	21 (15.4%)	23 (35.4%)	0.0018
Efficacy Population (N=108)	10 (9.3%)	19 (33.3%)	0.0003

^a Logistic regression model that included terms for the main effects of treatment group and primary tumor types (solid vs. hematologic).

Efficacy population noted above consisted of patients who were randomly assigned to a treatment group, were in the study for more than 28 days and had received chemotherapy.

A separate Quality of Life (QOL) report was included as an appendix in the study report. Self report QOL questionnaires were administered on day 1 and at weeks 4, 8, and 12 of the double blind study phase; only data from the baseline and week 12 assessments were analyzed. QOL assessments conducted using selected measures from the EORTC-QLQ-C30 questionnaire. Although this instrument measures 15 separate QOL constructs, as per the analysis plan developed *a priori*, primary QOL endpoints were specified as the Physical Functioning, Fatigue and Global Health Status/QOL scales.

The following table lists the QOL analysis population while consisted of 133 subjects:

Table 22: QOL analysis:

	Epoetin Alfa	Placebo	Full Cohort
Clinical ITT Population	136	65	201
No Baseline QOL Data (%)	16 (11.8)	8 (12.3)	24 (11.9)
Died on Study (%)	5 (3.7)	1 (1.5)	6 (3.0)
No Week-12 QOL Data (%)	29 (21.3)	9 (13.9)	38 (18.9)
QOL Analysis Population (%)	86 (63.2)	47 (72.3)	133 (66.2)

Amgen presented the following table showing the week-12 change scores for the primary QOL endpoints, adjusted for baseline differences using least-squares means. Although only the fatigue score appeared to show improvement over the twelve week period in the placebo group, the difference was not statistically significant compared to placebo as shown by Amgen's table reproduced below.

Table 23: Sponsor's Table: Adjusted Mean QOL Change Scores Baseline to Week 12, by Treatment Group

	N	Mean	Std. Err.	p-value
Epoetin Alfa				
Physical Functioning*	84	5.90	4.75	0.217
Fatigue†	85	-10.92	5.10	0.034
Global Health Status/QOL*	83	0.95	5.05	0.852
Placebo				
Physical Functioning*	47	4.31	5.54	0.438
Fatigue†	47	-6.84	5.97	0.254
Global Health Status/QOL*	46	2.48	5.55	0.655
Difference				
Physical Functioning*	131	1.59	4.68	0.735
Fatigue†	132	-4.08	5.02	0.419
Global Health Status/QOL*	129	-1.54	4.37	0.725

* Higher scores indicate better QOL

† Higher scores indicate worse QOL

Safety: Overall, treatment-emergent adverse events were reported in 59% of epoetin alfa-treated subjects and 65% of placebo-treated subjects. In general, the types and frequency of adverse events were similar between treatment groups. There were eight deaths in the epoetin alfa group (6%) and three deaths in the placebo group (5%) during the double-blind portion (first 84 days or within 30 days of discontinuation or completion) of the study. In most subjects, the cause of death was disease progression, and in no subject was the cause of death classified as possibly related to study drug. Treatment emergent serious adverse events were reported by 26% (35) epoetin alfa-treated subjects and 29% (19) placebo-treated subjects. The most common event was tumor progression; 12 (9%) in ESA group and 4 (9%) in the placebo group. Notably, "deep thrombophlebitis" appears in the listing in 5 ESA treated subjects and none in the placebo group. Fifteen epoetin alfa treated subjects (11%) and three placebo-treated subjects (5%) were withdrawn from the study because of adverse events. The following table lists the subjects who discontinued due to adverse events during the double blind phase.

Table 24: TVE Events:

Subject	Sex	Age (yrs)	Adverse Event	Day of Event ^a	Duration	Severity	Drug Relationship ^b
Epoetin alfa-treated subjects							
32 ^c	F	66	Cerebral hemorrhage ^d	71	Persisted	Moderate	Unlikely
43	M	69	Thrombophlebitis, deep ^d	18	Persisted	Marked	Probable
124 ^c	M	75	Disease progression ^d	14	Persisted	Marked	Unlikely
167 ^c	F	69	Disease progression ^d	76	Persisted	Marked	Unlikely
170	F	66	Pleurisy ^d	34	13 days	Marked	Possible
			Pulmonary embolism ^d	34	13 days	Marked	Probable
172	F	53	Thrombophlebitis, deep ^d	15	Persisted	Marked	Unlikely
178 ^c	M	70	Convulsions ^d	41	18 days	Marked	Unlikely
			Disease progression ^d	29	30 days	Marked	Unlikely
194 ^c	F	72	Heart disorder ^d	19	5 days	Moderate	Unlikely
235	M	73	Erythematous rash	23	Persisted	Moderate	Unlikely
			Dizziness	23	Persisted	Moderate	Unlikely
			Confusion	23	Persisted	Moderate	Unlikely
			Nausea	23	Persisted	Moderate	Unlikely
246	F	46	Thrombophlebitis, deep ^d	11	8 days	Marked	Unlikely
250	F	74	Thrombophlebitis, deep ^d	22	1 day	Marked	Probable
265 ^c	F	78	Disease progression ^d	31	Persisted	Marked	Unlikely
273	F	76	Skeletal pain	23	28 days	Moderate	Probable
			Depression	23	28 days	Moderate	Unlikely
			Leg pain ^d	23	28 days	Moderate	Probable
340	F	55	Hypertension ^d	54	7 days	Marked	Unlikely
344 ^c	F	61	Disease progression ^d	80	Persisted	Marked	Unlikely
Placebo-treated subjects							
84 ^c	F	54	Vomiting, nausea, ascites (disease progression) ^d	75	14 days	Moderate	Unlikely
145 ^c	F	73	Flu-like symptoms	3	14 days	Mild	Possible
201 ^c	F	71	Disease progression ^d	49	Persisted	Marked	Unlikely

^a Relative to day of first dose of study drug.

^b According to the investigator.

Review Comments:

The following table is generated from the data using FDA statistical review:

Table 25: Proportion of Patients transfused by baseline hemoglobin category:

Study Arm (No. of patients)	Baseline Hb < 9 g/dL	Baseline Hb ≥ 9 g/dL	Baseline Hb < 10 g/dL	Baseline Hb ≥ 10 g/dL	Baseline Hb < 11 g/dL	Baseline Hb ≥ 11 g/dL
ESA number transfused/ number in group	3/18 (17%)	7/118 (6%)	7/49 (14%)	3/87 (3%)	8/49 (16%)	2/87 (2%)
Placebo number transfused/ number in group	4/6 (67%)	17/59 (29%)	17/29 (59%)	3/36 (11%)	21/29 (72%)	0/36
Total transfused/total Number of pts	7/24	24/177	24/78	6/123	29/78	2/123

As can be seen from the above table, 123 of the 201 total patients had baseline hemoglobin levels above 11 g/dL, and very few of them needed transfusions. (b) (4)

Twenty five subjects in the study did not receive chemotherapy in violation of the protocol and of these 19 were in the ESA group. Such an imbalance can have serious negative impact on the ability to draw any conclusions from the study.

There was no improvement in QOL in either arm. The instrument was a multiple construct instrument, not an acceptable method to assess the impact of ESA on health related quality of life. The QOL cohort included only 133 (66%) of the 201 patients. In the cohort of 133 patients who were evaluable for QOL parameters, 6 in the ESA group and 3 in the placebo group did not receive chemotherapy. The study did not evaluate tumor endpoints.

(8) EPO-INT-10

Title of Study: A Double-Blind, Placebo-Controlled Study to Assess the Effect of Early Intervention and/or Treatment with Epoetin Alfa on Anemia in Cancer Patients Receiving Non-Platinum Containing Chemotherapy

Studied Period (years): 29 July 1996 through 13 August 1998

Date of Clinical Study Report: 12 March 1999

Objectives: The purpose of this study was 1) to assess the effect of early intervention or treatment with epoetin alfa on transfusion requirements and anemia in subjects receiving non-platinum-containing chemotherapy for non-myeloid malignancies; 2) to establish whether changes in erythropoietin and hemoglobin levels after two weeks, serum ferritin levels after two weeks, and changes in hemoglobin levels and reticulocyte counts after either two or four weeks predicted responsiveness to epoetin alfa therapy; and 3) to assess the benefits on quality of life, particularly fatigue, associated with the use of epoetin alfa.

Methodology: This trial was a multicenter, randomized (ESA to placebo ratio 2:1), double-blind, placebo-controlled study conducted in 15 European countries. To enroll subjects thought to be at high risk for the development of transfusion-dependent anemia, enrollment was restricted to subjects who had either low baseline hemoglobin levels (≥ 10.5 g/dL) at any time during chemotherapy or to those subjects whose hemoglobin had fallen substantially (≥ 1.5 g/dL per cycle or per month) since the beginning of the current course of chemotherapy such that it dropped to ≤ 12 g/dL. Subjects were stratified by tumor type (solid vs hematological) and hemoglobin level (≤ 10.5 g/dL vs > 10.5 g/dL). Treatment was to continue for 12 to 24 weeks (or three to six chemotherapy cycles), plus four weeks post-chemotherapy. QOL measurement was carried out using FACT-An, CLAS, and SF36. 55 item FACT-An questionnaire which contains 34 question FACT-G and 21 item anemia questionnaire. Thirteen of the 21 anemia related questions provide a separate fatigue subscale. The questions were to be administered at four time points during the study 1) pre-treatment, 2) week 4 or before the start of the second cycle of

chemotherapy, 3) week 16 (before the start of the 5th on study chemotherapy and 4) at trial completion or at the time of early study withdrawal. Five QOL scales were chosen *a priori* for analysis: FACT-G, FACT-An Fatigue subscale and three CLAS (Energy, Daily Activities and Overall Quality of Life). Additional two measures were also chosen for analysis: SF-36 physical component (PCS) and mental component (MCS).

Number of Subjects (planned and analyzed): 360 planned; 375 analyzed.

Diagnosis and Main Criteria for Inclusion: Subjects were to be ≥ 18 years old, with a confirmed diagnosis of non-myeloid malignancy for which non-platinum-containing chemotherapy was underway or imminent, with a performance score (ECOG) of 0, 1, 2, or 3 (i.e., not completely disabled) and a life expectancy of at least six months, and with a baseline hemoglobin ≤ 10.5 g/dL, or a fall in hemoglobin level ≥ 1.5 g/dL per cycle or per month since the beginning of the current course of chemotherapy such that it dropped to ≤ 12.0 g/dL. Subjects were not to have been previously treated with platinum-containing chemotherapy within the previous 3 months prior to study entry.

Dose and Mode of Administration, Epoetin alfa (Eprex or Erypo) at 150 IU/kg, s.c., t.i.w.; if, after four weeks of therapy, a subject's reticulocyte count increased $< 40,000/\mu\text{L}$ above baseline or the hemoglobin level increased by less than 1 g/dL above baseline, the initial dose (150 IU/kg t.i.w.) was to be doubled to 300 IU/kg t.i.w. If, at any time during the study, the hemoglobin level exceeded 15 g/dL, study drug was to be withheld until the hemoglobin level fell below 12 g/dL, and was to be restarted at a dose level approximately 25% below the dose level that was previously being administered.

Primary Endpoint: Transfusion requirements after first four weeks of treatment.

Secondary evaluations included changes in hemoglobin levels, hematocrit levels, reticulocyte counts, predictive algorithms for response, and quality-of-life parameters.

An amendment dated August 11, 1998 added post-study survival status assessment at two time points during the post-study period (15th November 1998 and 15th August 1999). The amendment states that the data will be reviewed and the results summarized for epoetin alfa and placebo arms will be reported separately from the main study report.

Patient Population:

Table 26: Diagnosis of Malignancies (Intent to Treat Population)

Diagnosis	Epoetin Alfa (N=251)	Placebo (N=124)	Overall (N=375)
Breast	78 (31%)	36 (29%)	114 (30%)
Non-Hodgkin's lymphoma	41 (16%)	21 (17%)	62 (17%)
Myeloma	37 (15%)	25 (20%)	62 (17%)
Hodgkin's lymphoma	19 (8%)	6 (5%)	25 (7%)
Chronic lymphatic leukemia	16 (6%)	5 (4%)	21 (6%)
Gastrointestinal ^a	17 (7%)	4 (3%)	21 (6%)
Ovarian	10 (4%)	7 (6%)	17 (5%)
Other ^b	10 (4%)	6 (5%)	16 (4%)
Lung	10 (4%)	3 (2%)	13 (4%)
Pancreas	5 (2%)	2 (2%)	7 (2%)
Prostate	4 (2%)	3 (2%)	7 (2%)
Sarcoma	2 (1%)	5 (4%)	7 (2%)
Unknown ^c	2 (1%)	1 (1%)	3 (1%)

^a Of the 21 subjects who had a gastrointestinal malignancy, 16 had a colon (8 epoetin alfa subjects, 4 placebo subjects), rectal (2 epoetin alfa subjects), or colorectal (2 epoetin alfa subjects) malignancy, 4 epoetin alfa subjects had a stomach malignancy and 1 epoetin alfa subject had an unknown gastrointestinal malignancy.

^b Includes tumor types that occurred in fewer than 3 subjects overall.

^c Malignancy of unknown primary origin.

Table 27: Patient Disposition:

	Epoetin Alfa (N=251)	Placebo (N=124)	Overall (N=375)
Intent-to-treat population	251 (100%)	124 (100%)	375 (100%)
Completed	155 (62%)	61 (49%)	216 (58%)
Not evaluable for efficacy	7 (3%)	9 (7%)	16 (4%)
Discontinued ≤28 days on study	6 (2%)	8 (6%)	14 (4%)
Subject choice	2	2	4
Other ^a	3	6	9
Death	1	3	4
Disease progression	1	2	3
Adverse event	1	0	1
All others	0	1	1
Lost to follow-up	1	0	1
Blind broken on treatment code ^b	1	1	2
Efficacy evaluable population	244 (97%)	115 (93%)	359 (96%)
Completed	154 (63%)	60 (52%)	214 (60%)
Discontinued >28 days on study	90 (37%)	55 (48%)	145 (40%)
Subject choice	16	18	34
Other ^a	70	37	107
Death	16	11	27
Disease progression	18	9	27
Stop or change in chemotherapy	19	7	26
Adverse event	11	4	15
Absence of response	2	2	4
All others	4	4	8
Lost to follow-up	4	0	4
Safety population	251 (100%)	124 (100%)	375 (100%)

^a Breakdown of categories under 'Other' was determined by the sponsor from the reason for discontinuation specified on the CRF by the investigator.

^b For one subject in each of the two treatment groups, the blind was prematurely broken on their treatment code resulting in their exclusion from the efficacy population; both subjects completed the study.

Efficacy Results:

The efficacy of epoetin alfa in treated subjects with anemia has been demonstrated in that the proportion of subjects transfused after Day 28 was significantly smaller in the epoetin alfa-treated group than in the placebo-treated group (p=0.0057, intent-to-treat; p=0.0168, efficacy). The proportion of subjects transfused after Day 28, regardless of the tumor type (solid or hematological) or baseline hemoglobin level (≤10.5 g/dL or >10.5 g/dL), was greater in the placebo group than in the epoetin alfa group.

The pharmacodynamic effect of epoetin alfa was also clearly demonstrated by significantly greater increases in hemoglobin and hematocrit (p<0.001) and in reticulocyte counts (p=0.037) from baseline to last visit in the epoetin alfa-treated arm compared with placebo.

At last assessment, the analysis of the change scores calculated between baseline and last assessment for five of the seven primary quality-of-life scales (the Total FACT-G, the FACT-An Fatigue, and the three CLAS scales), showed significant advantages for subjects randomized to epoetin alfa compared with placebo. A strong, positive association was found between the seven primary quality-of-life scale scores and hemoglobin levels, as well as strong associations between changes in hemoglobin levels and quality-of-life scores.

Review Comments: Besides the caveat of using multiple broad based QOL assessments, according to CSR, page 1520 of 1852, "a large percentage of subjects (approximately 45%; data not shown) had only one or two follow-up QOL assessments. Hence the QOL analyses were based on change from baseline to last assessment scores. The last observation carried forward approach constitutes a major impediment to interpreting the results of QOL studies. Additionally, QOL questionnaires were not available in all languages. For example, Fact-An and SF-36 were administered in six languages while CLAS questionnaire was administered in 10 languages. In other words, patients in some centers were entirely excluded.

The following table shows the QOL Analysis Population as per Amgen:

Table 28: QOL Analysis Population:

	Any QOL	FACT-An/SF-36	CLAS
Clinical ITT Population	375	375	375
No Translation of QOL Questionnaire	0	54	0
No QOL Data	4	2	7
Missing Baseline or Follow-up QOL Data	22	21	33
QOL Analysis Population	349	298	335

The following is the QOL analysis population by treatment group:

Table 29: QOL Analysis Population by Treatment Group:

	Epoetin Alfa	Placebo	Total
QOL Analysis Population	238	111	349
Died On Study	32	15	47

The following table states the study completion status of the QOL population by Treatment Group (page 1523 of CSR).

Table 30: Study Completion Status of QOL Population

	Epoetin Alfa N=239	Placebo N=111	Overall N=349
Lost to Follow	4 (1.68%)	0 (0.00%)	4 (1.15%)
Subject Withdrawal	11 (4.62%)	16 (14.41%)	27 (7.74%)
Death	32 (13.45%)	15 (13.51%)	47 (13.47%)
Other	41 (17.23%)	20 (18.02%)	61 (17.48%)
Study Completion	150 (63.03%)	60 (54.05%)	210 (60.17%)

As per Amgen, "about 47% (data not shown) of the 210 subjects who completed the study have only one or two follow-up QOL assessments". Amgen also has the following statements in the CSR (pages 1519-1520): "Ideally, as suggested by the US Food and Drug Administration (FDA), the longitudinal analysis of QOL data collected in a clinical intervention trial should incorporate linear mixed effects and/or GEE (general estimation equation) models. These models are of a repeated-measures design where the follow-up assessments are dependent variables and frequently, where the baseline assessment is included in the model as a covariate (i.e. independent variable). Unfortunately, these models do not work well when there are few repeated measures on a single subject. On this study, a single subject can have a maximum of three follow-up QOL assessments, with a large percentage of subjects (approximately 45%; data not shown) having only one or two follow-up assessments (e.g. assessment at week 4 and last assessment). For all these reasons, and because the relevant clinical secondary endpoints (i.e., changes in hemoglobin level, hematocrit level and reticulocyte count) were also evaluated at last assessment, it was decided to focus on QOL analyses upon the last assessment change scores."

In summary, the validity of the instruments, the data collection method, the number of missing data and the method of assessment, all point to significant problems in interpretation of this data and accepting Amgen's conclusions that there was a significant improvement in 'Quality of Life' in patients on the ESA arm.

SAFETY RESULTS: The incidence of adverse events was similar between the epoetin alfa and placebo groups with the most frequently reported adverse events being fever, aggravated malignant neoplasm (disease progression), nausea, granulocytopenia, constipation, leukopenia, and abdominal pain. The incidence of serious adverse events (34% epoetin alfa, 36% placebo) and discontinuations due to adverse events (15% epoetin alfa, 15% placebo) was also similar between the two treatment groups, and the incidence of deaths was slightly lower in the epoetin alfa group compared with the placebo group (14% epoetin alfa, 18% placebo). Of the subjects who discontinued the study (drop-outs), the most common reasons for discontinuation were death and disease progression. The percentage of subjects who discontinued due to death was

slightly lower in the epoetin alfa group (50%) compared with the placebo group (64%). Similarly, the percentage of subjects who discontinued due to disease progression was slightly lower in the epoetin alfa group (26.5%) compared with the placebo group (27.3%). More than one half of the subjects who died in both the epoetin alfa and placebo groups (53% and 59%, respectively) died while on study. Of the subjects who died, 25 (74%) in the epoetin alfa group and 17 (77%) in the placebo group died within 0-10 days after receiving their last dose of study drug. The most frequent adverse event reported in the subjects who died was aggravated malignant neoplasm (56% of subjects in the epoetin alfa group, 68% of subjects in the placebo group), reflective of their underlying disease.

Survival: As per Amgen, although the study was not designed with mortality as an endpoint, overall Kaplan-Meier estimates of survival measured up to three months after the last subject completed the study, showed a statistically significant result in favor of the epoetin alfa-treated group. The estimated median survival duration was 16.8 months for the epoetin alfa-treated group and 10.7 months for the placebo group. The estimated hazard ration was 1.38 (95% CI 1.03 to 1.85) indicating that the risk of death for placebo-treated subjects is 1.38 times the risk of death for epoetin alfa-treated subjects. Survival by tumor type was consistent with overall findings showing a trend in favor of the epoetin alfa-treated group.

Review Comments: Amgen cites the above results based on follow-up conducted 3 months after the last patient completed the study (Nov. 15, 1998). As per the protocol amendment noted above, survival information was to be collected one year after the last patient completed the study (August 15, 1999). It is not clear why the later follow-up information has not been presented or included in the current submission.

Review Comments on the study as it relates to determining the level of hemoglobin at which to initiate ESA:

The following table is generated from the data using FDA statistical review:

Table 31: Proportion of Patients transfused by baseline hemoglobin category:

Study Arm (No. of patients)	Baseline Hb < 9 g/dL	Baseline Hb ≥ 9 g/dL	Baseline Hb <10 g/dL	Baseline Hb ≥ 10 g/dL	Baseline Hb <11 g/dL	Baseline Hb ≥ 11 g/dL
ESA number transfused/ number in group	17/45 (38%)	29/206 (14%)	35/129 (27%)	11/122 (9%)	44/129 (34%)	2/122 (2%)
Placebo number transfused/ number in group	12/32 (38%)	24/92 (26%)	28/78 (36%)	8/46 (17%)	34/78 (44%)	2/46 (4%)
Total transfused/total Number of pts	29/77	53/298	24/78	19/168	78/207	4/168

As seen from above table, only 2 (4%) patients in the placebo arm required transfusion at hemoglobin levels at or above 11. The impact of ESA use was equally evident if ESA was initiated at hemoglobin ≤ 10 or at hemoglobin ≤ 11 g/dL.

An exploratory analysis was performed by the statistical reviewer Dr. Lee on median survival based on hemoglobin at study entry. The overall median survival was 22.3 months for ESA vs. 20.6 months for placebo who had baseline hemoglobin levels of ≥ 11 g/dL and 16.8 months vs 10.7 months for those with baseline Hgb < 11 g/dL. Median survival times were 19.5 months and 8.1 months for EPO and placebo-treated patients, respectively with a hazard ratio of 0.64 (95% CI 0.45, 0.91) among those with a baseline hemoglobin level of < 10 g/dL. Please see statistical review by Dr. Lee. While this *post-hoc* analysis is truly exploratory, if one were to draw even a remote inference, it would point out that initiation of ESA at hemoglobin < 10 g/dL could be safer [REDACTED] (b) (4)

(9) Study MR 92013/MR 02685

In the application Amgen submitted an incomplete study report MR92013 that had only the first 114 pages of the study report and did not contain any of the appendices, including study protocols, summary tables, data listings. These report consisted of the results from three similar protocols I88-036, 87-018 (OEO-U24), 87-019 (OEO-U25) and were three of the eight studies submitted in support of the supplemental approval of Procrit for treatment of anemia due to chemotherapy in patients with cancer. The protocols originally included 132 patients but based on concerns raised by the Agency on the pooling efficacy results obtained with an ESA other than Procrit (i.e. Eprex), the data from 59 patients receiving exclusively Procrit were analyzed and were presented in report 92013 at the time of efficacy supplement seeking labeling expansion for this new claim. Upon FDA request for the complete study report, Amgen provided the complete study report MR 02685. This report also includes information on subjects treated with an ESA other than Procrit (i.e. Eprex) and thus includes information on all the subjects treated under these 3 identical protocols. It should be noted that the combined subject level data provided in this submission included information on all 132 patients and not the just the 59 Procrit treated patients. Information contained in report MR02685 is briefly summarized here.

Study Title: A double-blind, placebo-controlled study to determine the safety and efficacy of Procrit administered subcutaneously in patients with anemia secondary to advanced cancer and cisplatin chemotherapy.

Study dates: October 1988 to July 1990.

Date of report: May 9, 1992

Number of patients 132 (67 Epoetin alfa, 65 placebo)

ESA dose 150 units/kg 3 times/week for 12 weeks or placebo in double blind phase

Key Entry Criteria: Hemoglobin ≤ 10.5 gm/dL within 7 days of study entry, non-myeloid malignancy being treated with aggressive chemotherapy regimen consisting of cisplatin.

Patient Disposition is shown below:

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Figure 2: Patient Disposition:

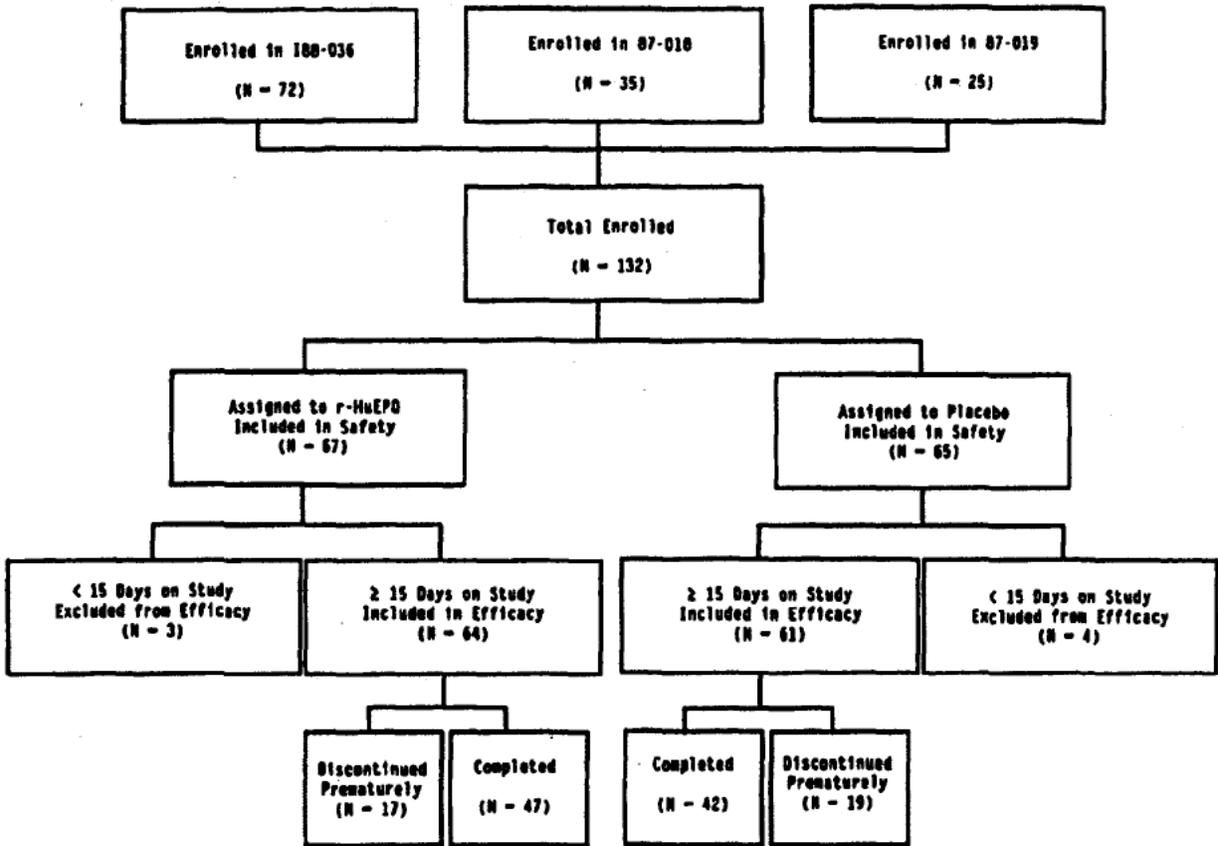


Table 32: Distribution of Primary Cancer:

Cancer Type	r-HuEPO (N = 64)		Placebo (N = 61)		Total (N = 125)	
	No.	%	No.	%	No.	%
Non-Hematologic	50	78.1	52	85.2	102	81.6
Lung, non-small cell	12	18.8	12	19.7	24	19.2
Gynecologic	8	12.5	10	16.4	18	14.4
Others	5	7.8	11	18.0	16	12.8
Lung, small cell	5	7.8	7	11.5	12	9.6
Gastrointestinal	7	10.9	4	6.6	11	8.8
Unknown Primary Site	6	9.4	1	1.6	7	5.6
Breast	2	3.1	3	4.9	5	4.0
Head and Neck	3	4.7	2	3.3	5	4.0
Esophagus	2	3.1	1	1.6	3	2.4
Prostate	0	0.0	1	1.6	1	0.8
Hematologic	14	21.9^a	9	14.8^a	23	18.4

Efficacy: The efficacy endpoint of reduction in transfusion requirements demonstrated efficacy of ESA for this endpoint.

Table 33: Proportion of Patients Transfused by Study Month:

Study Period	ESA	Placebo
	N transfused/ total (%)	N transfused/total (%)
Month 1	28/64 (44%)	27/64 (44%)
Month 2	12/56 (21%)	27/55 (49%)
Month 3	8/47 (17%)	13/46 (28%)
Month 2 & 3 combined	15/56 (27%)	31/55 (56%)

Safety:

Fifty eight (86%) ESA treated and 58 placebo treated patients (89%) reported adverse experiences during double-blind therapy. Among adverse events occurring with more than 10% frequency in the ESA group that exceeded the incidence rate in the placebo-treated group were edema (13%; placebo 9%), paresthesia (10%, placebo 8%) injection site reaction (10%; placebo 6%) abdominal pain (10%; placebo 5%), constipation (10%, placebo 5%) and rash (10%; placebo 3%)

Patients who discontinued treatment due to adverse events are summarized below:

Table 34: Deaths in the double blind phase of the study:

Patient No.	Treatment	Age	Sex	Duration of Therapy (Days)	Date of Last Dose	Date of Death	Intercurrent Illness	Relationship to Therapy
503	r-HuEPO	64	F	31	11/30/88	12/01/88	Pneumonia	None
702	r-HuEPO	69	F	25	06/02/89	06/03/89	Cardio-respiratory Arrest	None
703	r-HuEPO	70	F	27	06/07/89	06/09/89	Pulmonary Hemorrhage	None
402	Placebo	72	M	20	04/18/89	04/22/89	Urinary Tract Obstruction	None
7239	Placebo	34	M	79	03/31/90	04/03/90	Pneumonia	None
42732	Placebo	51	M	46	03/10/90	03/15/90	Metabolic Encephalopathy	None
49766	Placebo	51	F	52	03/07/90	03/08/90	Respiratory Failure	None

Table 35: Serious Adverse Events:

Patient No.	Serial Number	Treatment Group	Age	Sex	Duration of Therapy (Days)	Adverse Experience
805	335-1	r-HuEPO	60	M	5	Questionable Seizure
1206	364-1	r-HuEPO	56	f	57	Seizure
1401	354-1	r-HuEPO	49	F	28	Seizure
42730	319-1	r-HuEPO	51	M	66	Deep Vein Thrombosis
45291	377	r-HuEPO	74	F	82	Hyperosmolar Nonketotic Syndrome
502	268	Placebo	75	M	82	Pulmonary Embolus
604	304-1	Placebo	62	M	93	Right Brachial Embolus
1002	297	Placebo	57	F	29	Deep Vein Thrombosis
1102	324	Placebo	61	M	34	Seizure

Quality of life was assessed by patient self-reporting of the following 3 questions; patients were only required to record their scores at the beginning and end of the study. Two sample t-tests were used to compare groups with respect to change in quality of life from baseline to end of study; in addition, paired t-tests were used to test within group changes.

The following table is generated from the data using FDA statistical review:

Table 37: Proportion of Patients transfused by baseline hemoglobin category

Study Arm (No. of patients)	Baseline Hb < 9 g/dL	Baseline Hb ≥ 9 g/dL	Baseline Hb <10 g/dL	Baseline Hb ≥ 10 g/dL	Baseline Hb <11 g/dL	Baseline Hb ≥ 11 g/dL
ESA number transfused/ number in group	6/17 (35%)	11/50 (22%)	14/46 (30%)	3/11 (27%)	16/46 (35%)	1/21 (5%)
Placebo number transfused/ number in group	14/23 (61%)	19/42 (45%)	25/49 (51%)	8/16 (50%)	30/49 (61%)	3/16 (19%)
Total transfused/total Number of pts	20/40	20/92	39/95	11/27	46/95	4/37

As seen, epoetin alfa was effective at reducing the proportion of patients requiring transfusions across all baseline hemoglobin levels, as compared to placebo-treated patients. ESAs appeared to be particularly effective in patients receiving cisplatin-based chemotherapy since it is effective in replacing renal generated endogenous erythropoietin. It is noteworthy that the use of cisplatin has declined now that alternative treatment regimens, which are less nephrotoxic, are available. Placebo-treated patients with more than 11 gram/dL of hemoglobin required less transfusion as would be expected. The fact that 37 of the 132 subjects had a baseline hemoglobin of greater than 11 when the hemoglobin entry criteria was ≤ 10.5 is surprising. No conclusions regarding a level at which ESA should be initiated can be made from this study.

(10) Study MR 92014/MR 02676

In the application Amgen submitted an incomplete study report MR92013 that had only 107 pages of and none of the appendices, including study protocols, summary tables, data listings were included. Upon request by the FDA, Amgen provided the complete study report MR 02685. This report includes information on subjects treated with ESA other than Procrit (i.e. Eprex). The protocols originally included 157 patients but based on concerns raised by the Agency on the use of ESA other than Procrit (i.e. Eprex), the data from those 72 patients receiving exclusively Procrit were analyzed and were presented in report 92014 submitted in the efficacy supplement to support labeling expansion for this indication. Since Amgen had included information on patients from report MR02676 in the combined subject level meta-datasets, this report is briefly summarized here.

Study Title: A double-blind, placebo-controlled study to determine the safety and efficacy of Procrit administered subcutaneously in patients with anemia secondary to advanced cancer and aggressive cyclic chemotherapy.

Study dates: October 1988 to June 1990.

Date of report: February 28, 1991

Number of patients 157 (81 Epoetin alfa, 76 placebo)

ESA dose 150 units/kg 3 times/week for 12 weeks or placebo in double blind phase. No dose escalation

Entry Criteria: Hemoglobin ≤ 10.5 gm/dL within 14 days of study entry, non-myeloid malignancy being treated with aggressive cyclic cytotoxic chemotherapy regimen not containing cisplatinum.

Figure 4: Disposition of Patients:

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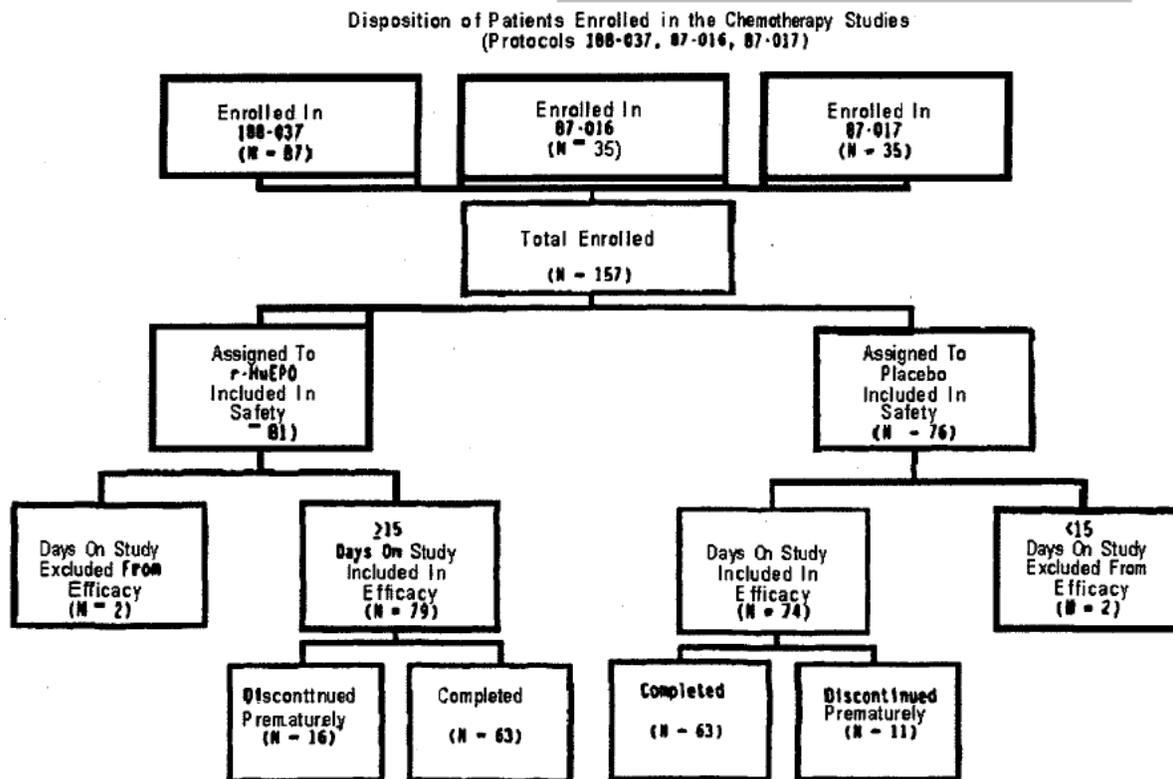


Table 38: Patient Disposition:

Disposition of Patients Enrolled in Chemotherapy Studies
 (Patients Evaluated for Safety in Protocols 188-037, 87-016, 87-017)

Patients ^a	r-HuEPO	Placebo	Total
Number Enrolled	81	76	157
Number (%) Completed ^b	63 ^c (78%)	63 ^d (83%)	126 (80%)
Number (%) Discontinued	18 ^e (22%)	13 ^e (17%)	31 (20%)
Adverse Experience	9 ^f	2 ^f	11
Death	0	3	3
Disease Progression	4	3	7
Protocol Violation	4	0	4
Physician/Sponsor Decision	1	2	3
Personal Reason	0	3	3

^a Patients were scored for only one primary reason for discontinuation as described in APPENDIX 5.

^b Patient completed double-blind therapy as determined by the investigator.

^c Six patients (#602, #606, #705, #903, #1102, #38612) completed double-blind therapy at less than 12 weeks. One patient (#904) discontinued double-blind therapy during Week 12.

^d One patient (#1303) completed double-blind therapy at less than 12 weeks.

The cancer types of the patients are shown below:

Table 39: Types of Primary Cancers

Cancer Type	r-HuEPO (N = 79)		Placebo (N = 74)		Total (N = 153)	
	No.	%	No.	%	No.	%
Non-Hematologic	43	54.4	45	60.8	88	57.5
Breast	14	17.7	18	24.3	32	20.9
Gynecologic	9	11.4	8	10.8	17	11.1
Gastrointestinal	7	8.9	4	5.4	11	7.2
Prostate	4	5.1	5	6.8	9	5.9
Lung, non-small cell	3	3.8	5	6.8	8	5.2
Lung, small cell	3	3.8	4	5.4	7	4.6
Unknown Primary Site	1	1.3	1	1.4	2	1.3
Head and Neck	1	1.3	0	0.0	1	0.7
Others ^a	1	1.3	0	0.0	1	0.7
Hematologic	36	45.6 ^b	29	39.2 ^b	65	42.5

Efficacy: The following table from Amgen shows the efficacy parameters of transfusion requirements.

Table 40: Transfusion Rates and Proportion of Patients Transfused:

**Mean Transfusion Rate and Proportion of Patients Transfused by Study Month
 (Patients Evaluated for Efficacy in Protocols 188-037, 87-016, 87-017)**

Study Period	r-HuEPO				Placebo			
	N	Patients Transfused No.	%	Mean Transfusion Rate ^a ± Std Err	N	Patients Transfused No.	%	Mean Transfusion Rate ^a ± Std Err
Month 1	79	20	25.3	79 0.69 ± 0.16	74	20	27.0	74 0.71 ± 0.16
Month 2	70	14	20.0	70 0.45 ± 0.15	68	19	27.9	68 0.77 ± 0.15
Month 3	62	9	14.5	62 0.39 ± 0.18 ^b	63	16	25.4	63 0.86 ± 0.18 ^b
Months 2 6 3	70	20	28.6	70 0.91 ± 0.27 ^c	68	25	36.8	68 1.65 ± 0.27 ^c

^a Least-squares mean from linear model analysis.
^b Between-group difference (p = 0.0726).
^c Between-group difference (p = 0.0561).

Amgen also reported quality of life results based on the same instrument used in Study MR 92013/MR 02685.

This results are shown below:

Table 41: QOL Measurements

Summary of the Change in Quality of Life Measures
 (Patients Evaluated for Efficacy in Protocols **188-037, 87-016, 87-017**)

Parameter (mm on 100 mm scale)	r-HuEPO (N = 63) ^a		Placebo (N = 61) ^a	
	Pre-Study	change ^d	Pre-Study	change ^d
Energy Level	41.75	9.86^c	45.38	2.97
Daily Activity	45.08	7.22^c	46.34	1.67
Overall Quality	52.22	5.68^d	52.34	-1.10

^a Pre- and post-study assessments were not available for all patients evaluated for efficacy (N = 79 r-HuEPO, 74 placebo).

^b There were no significant between-group differences in the change from pre- to post-study ($p > 0.05$).

^c Significant ($p \leq 0.05$) within-group change pre- to post-study.

^d Within-group change ($p = 0.08311$ from pre- to post-study).

Review Comments: The same review comments as for the cisplatin study (Study MR 92013/MR 02685). The quality of life instruments are vague and the statistical methods rudimentary. No conclusions can be drawn from these data.

Safety:

Adverse events that occurred in more than 10% of epoetin alfa patients that were greater than those in placebo patients were: pyrexia (31% vs placebo 20%), diarrhea (22% vs 11%), cough (17% vs placebo 8%), edema (16% vs 8% for placebo), upper respiratory infection (12% vs 8% for placebo) and diaphoresis (11% vs 1% for placebo). Eleven subjects discontinued therapy because of adverse events (9 in epoetin alfa arm and 2 in placebo). Ten patients died either on study or within one month of discontinuation of double blind therapy.

Review Comments on the study as it relates to determining the level of hemoglobin at which to initiate ESA:

The following table is generated from the data using FDA statistical review:

Table 42: Proportion of Patients transfused by baseline hemoglobin category

Study Arm (No. of patients)	Baseline Hb < 9 g/dL	Baseline Hb ≥ 9 g/dL	Baseline Hb <10 g/dL	Baseline Hb ≥ 10 g/dL	Baseline Hb <11 g/dL	Baseline Hb ≥ 11 g/dL
ESA number transfused/ number in group	11/28 (36%)	12/53 (23%)	15/54 (28%)	7/27 (26%)	22/54 (41%)	0/27
Placebo number transfused/ number in group	8/22 (38%)	18/54 (33%)	18/48 (38%)	8/28 (29%)	23/48 (48%)	3/28 (11%)
Total transfused/total Number of pts	18/50	30/107	33/102	19/55	45/102	3/55

As can be seen epoetin alfa had a very modest effect on reduction of transfusion requirements. From this truly exploratory exercise, the most effect was seen in patients with baseline hemoglobin of ≤10 g/dL. It is noteworthy that 55 of the 157 subjects had a baseline hemoglobin of greater than 11 g/dL when the hemoglobin entry criteria was ≤10.5 g/dL.

(11) Study PR98-27-008

This study was the basis of approval of Procrit/Epogen for weekly dosing for treatment of chemotherapy induced anemia in patients with non-myeloid malignancies. It was extensively reviewed by this reviewer at the time of approval for weekly dosing on 6/30/2004. This review can be found at

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist by searching under Procrit STN 103234/5053

Study PR-98-27-008 was a multi-center, randomized, double-blinded, placebo-controlled study conducted by NCCTG centers in the North Central United States and Saskatchewan, Canada. The planned enrollment was 330 subjects with anemia who were receiving myelosuppressive cytotoxic chemotherapy for advanced cancer. Eligible patients were randomized in a 1:1 ratio to epoetin alfa or placebo treatment, with stratification by center (investigator), type of primary cancer (lung, breast, or other), planned concurrent radiation therapy (yes vs. no), and degree of

anemia (hemoglobin < 9 g/dL vs. ≥ 9 g/dL). The double-blind treatment was administered for a maximum of 16 weeks, after which the subjects were followed for one year from the time of randomization for event monitoring (death, new primary malignancies, and long-term toxicities). The dose of double-blind study medication (40,000 IU of epoetin alfa or corresponding volume of placebo) was to be administered by s.c. injection, once weekly. If after 4 weeks of therapy hemoglobin (Hgb) concentrations had not increased by > 1 g/dL or if the subject had received a transfusion during the first 4 weeks of therapy, the weekly dose of study drug was to be increased to 60,000 IU once weekly. If, at any time during the study, the Hgb concentration exceeded 15 g/dL, Hgb was to be determined one week later. If the Hgb exceeded 15 g/dL, study drug was to be withheld and Hgb was to be determined weekly until it fell below 13 g/dL. Study drug was then to be restarted at a dose level 25% less than that previously administered. During double-blind treatment, subjects were to receive a daily oral iron supplement. All subjects could receive RBC transfusions at the discretion of the physician. A Hgb determination was to be obtained at the time of transfusion. Subjects who discontinued chemotherapy during the double-blind period were to continue the study treatment through 16 weeks. The efficacy and safety results have been described in the previous review at the time of approval. The question of transfusion requirements by baseline hemoglobin is explored here.

The following table is generated from the data using FDA statistical review:

Table 43: Proportion of Patients transfused by baseline hemoglobin category

Study Arm (No. of patients)	Baseline Hb < 9 g/dL	Baseline Hb ≥ 9 g/dL	Baseline Hb <10 g/dL	Baseline Hb ≥ 10 g/dL	Baseline Hb <11 g/dL	Baseline Hb ≥ 11 g/dL
ESA number transfused/ number in group	8/52 (15%)	8/121 (6.6%)	15/122 (12%)	1/52 (1.9%)	22/54 (41%)	0/52
Placebo number transfused/ number in group	17/53 (32%)	19/118 (16%)	27/123 (22%)	9/47 (29%)	23/48 (48%)	0/47
Total transfused/total Number of pts	25/105	27/239	42/245	10/99	52/245	0/99

As can be seen none of the subjects in the study with baseline hemoglobin above 11 required transfusion. Epoetin alfa treatment showed a consistent benefit of reduction in transfusion requirement compared to placebo when baseline hemoglobin was below 10 or 9 and less so at higher baseline hemoglobin. From this truly exploratory exercise, the most effect was seen in patients with baseline. The overall survival was similar to placebo across various hemoglobin thresholds except for baseline hemoglobin ≤ 9 gm/dL where it was shorter (8.6 vs. 12.3). The PFS was also likewise similar to placebo. A retrospective exploratory analysis such as this can not help in determining a precise hemoglobin level at which ESA could be initiated. There was no demonstrable improvement in quality of life assessment sin this study. Further details can be found in the original review.

(12) EPO-CAN-15

This study was not included in the subject level combined analysis. Amgen refers to it in the submission as having been added to the Cochrane meta-analysis. Amgen included a partial report in the initial submission. Upon request, Amgen provided this clinical study report on June 13, 2008 submission.

Title of Study: A randomized, double-blind, placebo-controlled study to evaluate the impact of maintaining hemoglobin levels using EPREX® (epoetin alfa) in limited disease small cell lung cancer (LD SCLC) patients receiving combined chemotherapy and radiation therapy.

Study Initiation/Completion Dates: First patient randomized August 22, 2001. Study suspended on September 29, 2003 and terminated on February 2004 based on the recommendation of the

Data Safety Monitoring Board (DSMB) due to an increased incidence of thrombovascular events (TVEs) in the epoetin alfa group.

Date of database lock: 3 May 2005

Clinical Study report date: 15 February 2008

Objectives: The objective of this study was to evaluate the impact of maintaining hemoglobin (Hb) in the range of 14 to 16 g/dL on disease progression-free survival using epoetin alfa or placebo in limited disease small cell lung cancer (LD SCLC) patients receiving combined modality chemoradiation therapy.

Primary endpoint: Progression-free survival

Secondary endpoints included the following: (1) Tumor response to first-line chemotherapy plus concurrent radiotherapy, (2) Median and overall survival, (3) Local disease progression, (4) Hb over time (baseline to study completion), (5) Proportion of patients receiving red blood cell (RBC) transfusions, (6) Quality-of-life change scores between epoetin alfa and placebo groups (measured with the Anemia Subscale and the Cancer Linear Analog Scale/Linear Analog Scale Assessment [CLAS/LASA]).

A protocol amendment in October 2002 revised the target Hb level (lowered to 12-14 g/dL, and study drug initiated at Hb < 13 g/dL).

Number of Subjects: The original sample size was 620 subjects (310 subjects in each group). Due to early termination of the study 104 intent to treat patients were analyzed for efficacy and 101 patients for safety.

Patient Population: Adult patients with Limited Disease – Small Cell Lung Cancer scheduled to receive a 4- or 6-cycle platinum-based plus etoposide chemotherapy regimen (plus possible additional non-investigational chemotherapy agents), combined with concurrent thoracic radiation therapy

Randomization ratio 1:1, stratified by center.

Hemoglobin at ESA initiation: ≤ 14 g/dL

Dose of ESA: starting dose 40,000 units SC weekly from day 1 of chemotherapy cycle; increased to 60,000 units if after 3 weeks Hb ≤ 14 g/dL. Withhold for Hgb > 14 g/dL, and restart at Hb ≤ 13 g/dL at 30,000 units if the subject was receiving 40,000 units and 40,000 units if the subject was receiving 60,000 units..

Duration of Treatment: Throughout chemotherapy and concurrent radiotherapy regimen, and continue through to prophylactic cranial irradiation (PCI), if administered (defined as the double blind, active treatment phase).

Follow up (non treatment phase) was planned for 5 years post randomization

Statistical Methods: After the study was terminated early, the analyses were modified to focus more on the evaluation of safety data. For the purpose of this report, demographic, subject disposition, study drug exposure, concomitant therapies, safety evaluations and limited efficacy parameters are included in the analysis. Descriptive statistical methods were used. Time to disease progression (TTP) was analyzed instead of PFS in light of smaller subject numbers. Kaplan-Meier estimates of both TTP and overall survival were obtained between treatment groups based on a Log-Rank test for equality over strata for all subjects.

To try to understand the observed imbalances between groups, specifically the observed imbalance in the occurrence of TVEs, an extensive investigation of these events in relation to potential explanatory factors was carried out. Although the numbers are too small to make statistically or clinically meaningful conclusions, exploratory analyses were conducted to try to elucidate any differences in safety and efficacy outcomes in the subject subgroups enrolled in the original protocol (pre-amendment) defined by a target Hb level of 14-16 g/dL and a requirement to start study drug at a Hb of < 14 g/dL, and those enrolled under the amended protocol defined by a target Hb level of 12-14 g/dL and a requirement to start study drug at a Hb < 13 g/dL. Subgroup analyses were performed on the following parameters; clinically significant treatment emergent TVEs, Hb over time, study drug exposure, TTP and overall survival.

Demographic and Baseline Characteristics:

A total of 104 LD SCLC subjects were randomized, 52 to epoetin alfa and 52 to placebo. Baseline characteristics (age, gender, race, smoking status, weight, height, vital signs, ECOG Performance status, laboratory values including Hb) were similar in the 2 treatment groups. The exception was the protocol version to which subjects were randomized: 33 epoetin alfa subjects and 23 placebo subjects randomized under the original protocol (target Hb 14-16 g/dL, study drug started at Hb <14 g/dL) versus 19 epoetin alfa subjects and 29 placebo subjects randomized under the amended protocol (target Hb 12-14 g/dL, study drug started at Hb < 13 g/dL). In both groups, the majority (84.6%) of subjects were 70 years of age or younger, the percentage of subjects with nodal disease was the same (21.2%) and 98.1% were known to be either current or former smokers. In the epoetin alfa group, 61.5% of subjects were male, compared to 53.8% in the placebo group.

Safety results:

The safety population included all subjects who received at least 1 dose of study drug (51 epoetin alfa and 50 placebo). For those subjects included in the safety population, the mean cumulative dose of study drug in the placebo group was 1.5 times greater than in the epoetin alfa group (4-cycle regimen: 706,607 units in placebo versus 511, 818 units in epoetin alfa; 6-cycle regimen: 994,483 units in placebo versus 646,897 in epoetin alfa). At the time enrollment was halted, a similar number of subjects among the safety population had completed treatment (31 epoetin alfa and 32 placebo).

Only Grade 3 and 4 adverse events (AEs) (National Cancer Institute (NCI): Common Toxicity

Criteria (CTC), Version 2.0) were to be reported in the study. The majority of subjects (96.0%) in the study reported at least 1 AE. Infection with and without accompanying neutropenia occurred in 29.7% of all subjects during study (31.4% in the epoetin alfa group and 28.0% in the placebo group). Pulmonary AEs were only seen in the epoetin alfa group (7.8% of subjects). Pain was reported more often in the placebo group (10.0% in the placebo group versus 3.9% in the epoetin alfa group). More placebo subjects (20.0%) experienced Grade 3 or 4 anemia compared to epoetin alfa subjects (3.9%). Twice as many subjects in the epoetin alfa group experienced gastrointestinal AEs compared to the placebo group (19.6% epoetin alfa versus 10.0% placebo). There were more AEs related to the cardiovascular system (includes cardiac and extra-cardiac TVEs) in the epoetin alfa group compared to placebo (39.2% in epoetin alfa subjects versus only 6.0% in placebo subjects). This was particularly notable in regards to thromboembolism occurrence, where 9 subjects experienced a TVE (17.7%) in the epoetin alfa group compared to none of the subjects in the placebo group.

Serious adverse events occurred in 62.8% of subjects in the epoetin alfa group, compared with 50.0% of subjects in the placebo group. The largest difference between treatment groups in the incidence of serious adverse events (SAEs) was seen in the category of cardiovascular events, which included thrombosis/embolism (19 subjects in the epoetin alfa group [37.3%] compared to 2 subjects in the placebo group [4.0%]). There were 18 subjects who reported clinically significant, treatment-emergent TVEs in the safety population (17.8% of 101 subjects): 16 subjects (31.4%) in the epoetin alfa group and 2 (4.0%) in the placebo group. Of the 16 epoetin alfa subjects who had TVEs, there were 4 deaths (CVA, MI, sepsis and pulmonary edema), 8 arterial TVEs and 4 venous TVEs. Four of the epoetin alfa subjects with arterial TVEs were myocardial infarctions that occurred during concurrent thoracic radiation. Of the 2 subjects who had TVEs in the placebo group, there was 1 death (MI) and 1 arterial TVE. No patterns in body weight, age, gender, baseline platelet count and timing of the first dose of study drug to the occurrence of TVE were observed.

In the epoetin alfa group, 14 of the 16 subjects who had TVEs (87.5%) occurred in subjects randomized under the pre-amendment protocol when study drug was initiated at a higher Hb level (< 14 g/dL) and a higher target Hb was intended (14-16 g/dL). In these cases, the mean Hb level at study drug initiation was 13.1 g/dL. In the remaining 2 subjects (12.5% of the TVEs occurred post-amendment), the mean Hb at study drug initiation was 12.6 g/dL.

When looking at a higher Hb level at the time of study drug initiation as a risk factor for TVE occurrence, a trend was observed at the threshold Hb level of 13 g/dL ($p=0.0956$). This trend was not seen when 12 g/dL was used as the threshold Hb level ($p=0.5508$). Changes from baseline in clinical laboratory results and vital signs in both epoetin alfa and placebo groups were small and not clinically significant.

A total of 57 deaths were recorded during the study; 28 deaths (53.8%) occurred in the epoetin alfa group compared to 29 deaths (55.8%) in the placebo group (overall mortality in the intent-to-treat (ITT) population). The majority of the deaths (80.7% overall) were reported as disease progression; 21 deaths due to disease progression in the epoetin alfa group (75% of deaths) compared to 25 deaths due to disease progression in the placebo group (86% of deaths). Across

both treatment groups, the age at time of death ranged between 39.1 years to 82.7 years, 35 males, and 22 females.

Efficacy results:

At the end of the final cycle, the overall tumor response rate for 39 of 52 subjects for whom data were available in the epoetin alfa group was 82.1% (30.8% complete response and 51.3% partial response). This was similar to the overall tumor response rate of 72.5% (30.0% complete response and 42.5% partial response) observed in 40 of 52 subjects for whom data was available in the placebo group. Six weeks after chemotherapy, the overall tumor response rate for 32 subjects in the epoetin alfa group was 87.5% (43.8% complete response and 43.8% partial response). This was similar to the overall tumor response rate of 78.9% (39.5% complete response and 39.5% partial response) observed in 38 subjects in the placebo group. No significant difference was observed in the Kaplan Meier estimates of the time to disease progression in both treatment groups. Median TTP in the epoetin alfa group was 15.8 months (95% confidence interval (CI), 11.3, 28.0) versus 16.5 months (95% CI: 14.6, 23.3) in the placebo group (not statistically significant, $P=0.633$). The hazard ratio for TTP in the epoetin alfa group relative to the placebo group was not significant [hazard ratio (HR) 1.13, 95% CI: 0.68, 1.88 ($P=0.634$)]. Subset analyses by protocol version (subjects randomized either pre- or post-amendment) also did not reveal any difference in time to disease progression in the Kaplan Meier estimates ($P=0.424$ and $P=0.837$, respectively). No significant difference was observed in the Kaplan-Meier estimates of OS between treatment groups ($P=0.644$). Median overall survival (OS) for the epoetin alfa group was 23.5 months (95% CI: 13.6, Not Estimable) versus 24.0 months (95% CI: 17.3, 30.7) for the placebo group ($P=0.83$). The hazards ratio for OS in the epoetin alfa group relative to the placebo group was not significant [HR 1.13, 95% CI: 0.67, 1.90 ($P=0.644$)].

There was a good separation of Hb levels between epoetin alfa and placebo treatment groups by Week 4 of the start of chemotherapy. Over time, the Hb level in the epoetin alfa treatment group was generally maintained between 12.5-14 g/dL, whereas the Hb level in the placebo group was only generally maintained between 10 - 11 g/dL. Compared to placebo, subjects in the epoetin alfa group received significantly fewer transfusions (17.3% versus 51.9%, $P < 0.0001$), and in the epoetin alfa subjects who did receive transfusions, a lower average number of units were transfused (2.4 units versus 5.3 units in the placebo group).

Review Comments: This study showed a high incidence of thrombovascular events since the goal was to achieve higher hemoglobin targets. It is consistent with higher incidence of thrombovascular events seen when a similar strategy was used, i.e., BEST study. The CAN-15 study was also prematurely terminated. Although studies aiming for higher hemoglobin levels do not contribute to the quest to explore what lowest hemoglobin level should one initiate ESAs, it is not clear why Amgen did not include this study in the combined subject level analysis. It is particularly surprising since Amgen did include BEST study into their analysis.

6 Review of Efficacy

Efficacy Summary

The purpose of this submission is for Amgen to revise and incorporate changes to the product label based on discussions at the May 10, 2007 Oncologic Drugs Advisory committee meeting as requested by the FDA in a letter dated May 30, 2007. This supplement is therefore intended to make modifications to the product label and not to seek a new indication. Specifically, this submission addresses the following items from the May 30, 2007 letter:

(1) FDA Item 3 of the letter: Revise the Indication statement to clarify the severity of anemia for which ESAs are indicated, i.e. pre-treatment hemoglobin level needed to initiate ESA therapy

(b) (4)

(2) FDA item 4 of the letter: Revise 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

(b) (4)

(3) FDA item 5 of the letter: Revise the Indications and Usage section and Dosage and Administration Section to indicate that ESAs should be discontinued following completion of concomitant chemotherapy regimen

(b) (4)

Amgen's justification for the proposal regarding the above first two items is reviewed here.

(b) (4)

In support of the first two items, Amgen provided exploratory, combined subject-level analyses of the results 11 studies utilizing epoetin alfa by reviewing the transfusion requirements at various baseline hemoglobin levels along with corresponding risk of death and clinically significant TVE. The studies included in Amgen's analyses are all the studies listed in Table 1 except Epo-CAN-15. Amgen provided corresponding combined datasets for these studies. All of these studies are described on an individual basis in section 5. It should be noted that the studies were not designed to evaluate the effect of baseline hemoglobin on outcome measures and such analyses are indeed exploratory.

In addition, Amgen proposes to make the following changes to the label:

1. [Redacted] (b) (4)
2. [Redacted] (b) (4)

Both these studies have been discussed in detail under discussion of individual studies in section 5, along with reviewer's rationale for not accepting Amgen's proposed changes to the product label.

Firstly, however Amgen's rationale for each item noted above in the FDA letter dated May 30, 2007 and this reviewer's assessment of the rationale is presented below:

(1) FDA letter Item 3

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)

Sponsor's results:

(b) (4)

(b) (4)

Reviewer's comments:

(b) (4)

Figure 5: (Sponsor's Figure) Death with Follow-up: Hazards Ratio by Baseline Hemoglobin (Placebo-controlled Epoetin alfa CIA Studies)

(b) (4)

Figure 6 (Sponsor's Figure) Clinically Relevant VTE: Hazards Ratio by Baseline Hemoglobin (Placebo-controlled Epoetin alfa CIA Studies)



Sponsor's Conclusion:

Amgen proposed [redacted] (b) (4)
[redacted]
[redacted]

Reviewer Comments:

Since this submission in December 2007, there have been two subsequent label changes made addressing this issue. In 2008 Oncology Drug Advisory Committee meeting, Amgen proposed initiation of ESA at baseline hemoglobin level of ≤ 10 g/dL. Amgen submitted a CBE on August 5, 2008 which has the wording [redacted] (b) (4) So this is no longer an issue. [redacted] (b) (4)
[redacted]



(b) (4)

Despite these caveats, the advantage in transfusion reduction appears to be maintained when ESA is initiated at Hb \leq 10 g/dL. The current product label submitted as CBE on August 5, 2008 is acceptable to the FDA and Amgen adequately describes the starting hemoglobin in that label.

The FDA statistical reviewer performed analysis of transfusion rates, overall survival and progression free survival for individual studies with different hemoglobin thresholds from the combined analysis data provided by Amgen. Please see statistical review by Dr. Lee. Her analysis is incorporated in the review of individual studies described here. Her overall conclusions are noted below:

(b) (4)

It is very difficult to draw conclusions from these data. Some studies had very few or no patients enrolled at lower baseline hemoglobin categories while other studies had very few or no patients at higher baseline hemoglobin categories.

(2) FDA Letter Item 4

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.

Sponsor's Results:

(b) (4)

Sponsor's Conclusion:

(b) (4)

FDA Statistical Reviewer's Comments:

Amgen's conclusion is based on meta-analysis results. As pointed out in the May 10, 2007 ODAC meeting, the agency provided several reasons against performing meta-analyses:

Reasons against doing a meta-analysis

- *Can obscure safety signals from individual studies*
- *Results depend on the studies included*
 - *Earlier meta-analyses suggested statistical significance on overall survival favoring ESAs*
 - *Later meta-analyses suggest statistical significance on overall survival favoring controls*
- *Cumulative meta-analyses and retrospective meta-analyses have issues on appropriate allocation of alfa*
- *Heterogeneous trials w/ variable quality, variable lengths of follow up, variable target Hgb, and heterogeneous tumor types*
- *Concentrate on the differences – e.g., longer follow-up for later studies, differences in target hemoglobin levels, and differences in patient populations*

(b) (4)

(b) (4)

Clinical Reviewer's Comments:

In addition to the statistical reviewer comments, it should be noted 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, (b) (4)

[Redacted text block]

In summary, Amgen has not provided adequate justification in this submission for their proposal (b) (4)

[Redacted text block]

[Redacted text block]

(b) (4) Hence, updating this information in the product label is not warranted.

(b) (4) N93-004 (b) (4) study was designed with a sample size of 400 patients to detect a non-inferiority margin of 15%. Since the study was terminated prematurely with enrollment of only 224 subjects, the non-inferiority inference is not valid. The information of the study was included in a previous version of the label, when there were no safety signals from any other studies and this was the only study where any results regarding tumor outcomes were available. (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

7 Review of Safety

Safety Summary

The labeling supplement also intends to convert the label into PLR format. To that extent Amgen provided a safety data set containing MedDRA coded adverse events from previously submitted studies. Amgen provided adverse drug reactions incidence data based on the following studies in order to determine which events were to be identified as adverse drug reactions (ADRs) of epoetin alfa. Adverse events data from the following double-blind, placebo controlled Procrit studies were reviewed by Amgen for generating the proposed ADR table for inclusion in the label. The adverse events identified in these studies were converted to MedDRA (version 10.1). Amgen provided the raw pooled data from these studies that were used in generation of ADR in subsequent submission (dated June 13, 2008; sequence 158).

Table 46:

Study Group	Label	Study Identifier	N	
			PROCRT	Placebo
All study groups			739	494
Oncology			237	238
Advanced cancer and aggressive cyclic chemotherapy	Oncology, on chemotherapy	188-037 ² 87-016 ² 87-017 ²	35	37
Advanced cancer and cisplatinium therapy	Oncology, on chemotherapy	188-036 ³ 87-018 ³ 87-019 ³	28	31
Once weekly dosing	Oncology, on chemotherapy	PR98-27-008 ⁴	174	170
HIV			144	153
HIV and AIDS; on AZT	HIV	87-020 ⁵ 87-021 ⁶ H87-037 ⁷ 188-009 ⁸	144	153
Surgery			358	103
Major orthopedic surgery	Surgery	M92-011 ⁹ N93-057 ¹⁰	358	103

AIDS = acquired immunodeficiency syndrome, AZT = zidovudine, CSR= clinical study report, HIV = human immunodeficiency virus, PLR = physician labeling rule

As noted before, the data supporting the changes in the label for non-oncology indications are being reviewed and addressed by Division of Hematology and Medical Imaging review staff.

Although Amgen included the above studies for generation of ADR tables, the exposure to Procrit was much different between the weekly dosing PR98-27-008 study (a sixteen week administration with a mean exposure of 49000 units/week and the other two studies (each with 3 similar protocols) that had a 12 week exposure with a mean exposure at week 12 of 396 units/kg/week in the cisplatinium containing chemotherapy and 368 units/kg/week in the non-cisplatinium containing chemotherapy protocols. Weekly dosing of Epogen/Procrit is also the standard of practice among practicing oncologists. Hence the revised label should reflect adverse drug reactions based on the weekly dosing study.

As noted before, the data supporting the changes in the label for non-oncology indications are being reviewed and addressed by Division of Hematology and Medical Imaging review staff.

Amgen submitted this labeling supplement with data and analyses geared only towards supporting the proposed label changes. Amgen did not provide an integrated analysis of safety.

Major safety issues with Epogen, however, include the adverse cancer outcomes as shown in several studies and are already included in the current label.

The following is the table of common adverse events occurring at $\geq 5\%$ per-patient incidence in the ESA arm and at a higher incidence than placebo in Protocol PR98-27-008, which this reviewer recommends for inclusion in the label:

Table 47: Adverse Events

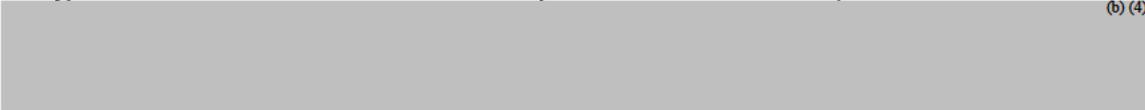
Adverse Reactions to Epogen		
MedDRA (10,1) Preferred term	Epogen (n = 168)	Placebo (n = 165)
Nausea	35%	30%
Vomiting	20%	16%
Myalgia	10%	5%
Arthralgia	10%	6%
Stomatitis	10%	8%
Cough	9%	7%
Weight decrease	9%	5%
Leukopenia	8%	7%
Bone pain	7%	4%
Rash	7%	5%
Hyperglycemia	6%	4%
Insomnia	6%	2%
Headache	5%	4%
Depression	5%	4%
Dysphagia	5%	2%
Hypokalemia	5%	3%
Thrombosis	5%	3%
Headache	5%	4%
Depression	5%	4%
Dysphagia	5%	2%
Hypokalemia	5%	3%
Thrombosis	5%	3%

8 Appendices

Labeling Recommendations: Amgen was provided FDA's proposal for a revised label. The suggested revisions also incorporate input for revisions from DMIHP review team. Agreement on final labeling was not reached with Amgen.

The major revisions are outlined 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 "events" throughout labeling.

2. Indications and Usage section

- a. New  (b) (4) "not indicated for" subsections created to limit repetition of the same information across multiple indications.
- b. Currently approved indications statements re-worded for brevity and clarity
- c. Titles of subsections shortened for brevity.

3. Dosage and Administration

- a. New  (b) (4) subsection created to limit repetition of the same information across multiple indications.
- b. Directions for patient monitoring deleted from this section to limit repetition; where necessary, such information is described under Warnings and Precautions (e.g., Hypertension, Laboratory Monitoring).
- c. Elimination of redundant text (e.g., both text and table provide essentially the same dosing directions for patients with chronic renal failure).
- d. Elimination of rationale for dosing directions (e.g., "response time of the hemoglobin to a dose increase can be 2 to 6 weeks") or preparation and administration (e.g., prolonged vigorous shaking may denature...").
- e. References to  (b) (4) deleted; these data are cited in context in the Clinical Studies section.
- f. 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.
- g. "maintenance dose" subsections deleted; information in these subsections generally overlap with information in the "dose adjustment" subsections, which were retained and re-worded for brevity and active voice.

4. Dosage Forms and Strengths

- a. Information in this section moved to section 16; remaining information shortened for brevity and consistency with other labeling.
- b. References to the (b) (4) deleted; (b) (4)

5. Contraindications

- a. Replaced contraindication regarding theoretical allergic reactions to subcomponents with more specificity to serious allergic reactions as report in post-marketing experience and in Warnings/Precautions.
- b. Added contraindication regarding benzyl alcohol containing formulations in given the availability of an alternative formulation and consistent with proposed wordings in other sections not to use the benzyl alcohol containing formulation in pregnant women, neonates and infants due to documented risks with other products.

6. Warnings and Precautions

- a. (b) (4)
- b. (b) (4)
- 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, references to the study phase (e.g., phase 3) deleted throughout this section, as superfluous to other information describing study design and as per FDA Guidance. Deleted alternate names of studies (e.g., ENHANCE) throughout sections 5.1 and 5.2, as per FDA Guidance on describing clinical studies.
- d. (b) (4)
- e. (b) (4)
- f. 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.
- g. (b) (4)

- h. [REDACTED] (b) (4)
- i. Section 5.3 (Hypertension) revised to limit redundant dosing information that can be addressed with cross-reference to D&A section. Also deleted unnecessary information [REDACTED] (b) (4)
- j. Moved up “Seizures” to section 5.4 as next most common serious adverse event. Deleted statement “while the relationship between seizures and rate of rise....” as unnecessary explanation; dosing recommendations already adequately covered in D&A section of labeling.
- k. Deleted section on “loss of response”. Product labeling should not including information related to general practice of medicine (i.e., differential diagnosis and diagnostic work-up of anemia).
- l. Revised subsection on PRCA to remove references to deleted subsection on loss of response; edited for brevity and active voice.
- m. Deleted subsection on Hematology. First paragraph redundant and covered in subsection on laboratory monitoring and D&A. Second paragraph does not rise to level of “warnings” and has been edited for brevity and moved to the Adverse Reactions section of the label. The third paragraph is general medical information, unrelated to the product and therefore deleted from product labeling. The fourth paragraph was deleted as it relates to unapproved uses.
- n. Subsection on risk in infants deleted- superseded by new Contraindications statement
- o. Subsection on Dialysis Management edited for brevity and critical information; theories on potential effects and absence of effects in clinical studies deleted as unnecessary information.
- p. Subsection on [REDACTED] (b) (4) 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. Analyses based on pooled datasets appear to underestimate effects observed in individual studies, thus these data have been deleted. Tables for individual studies should delete any rows in which events were more frequent in the control arm than placebo and remaining adverse reactions should be listing in decreasing incidence, based on rates in the Epogen arm.
- b. FDA cannot verify data in this table because SAS datasets not supplied (only program files). Please supply SAS transport files and a tabular summary of all adverse events.
- c. Hypertension subsection for patients with CRF deleted-to limit redundancy this information is now contained in the Warnings/Precautions subsection on hypertension.
- d. In the subsection on adverse events in cancer patients, data from the three-times-per week regimen across six studies was excluded because the small size and heterogeneity which may obscure safety signals and limit truly random allocation as well as the lower drug exposure when compared to the weekly dosing schedule.
- e. In the subsection on adverse events in patients scheduled for surgery, data on the SPINE study deleted to limit redundancy- these data are described in the new section 5.1

- f. Post-marketing section: Revised to include (b) (4) porphyria; this replaces section in precautions that contains no data on incidence and thus appears to be post-marketing reports. Revised section on allergic reactions for brevity and cross-reference more detailed information in the Warnings and Precautions subsection.
- g. Immunogenicity subsection: This section contains no data- please see FDA comments regarding provision of data or revision to state that data are not available from clinical studies.

8. Drug Interactions

- a. Section revised to clarify that no drug-drug interactions studies have been performed/provided to FDA for this product.

9. Use in Specific Populations

- a. Pregnancy Category C: Editorial changes. Added reference to Contraindications and information on risks of benzyl alcohol in premature infants.
- 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. Reference to Contraindications section added.
- c. Pediatric Use: Addition of reference to the Contraindications section and statement that benzyl-alcohol containing formulations should not be used in infants/neonates. Information on study in children with cancer deleted as this study is described in the Clinical Studies section (14). Re-worded for clarity.
- d. Geriatric Use: see FDA embedded comment regarding revision to reflect 5 clinical studies. Additional changes for clarity.

10. Overdosage

- a. 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.

11. Description

- a. Statement regarding “same biological effects as endogenous erythropoietin” deleted since this is already stated in the Clinical Pharmacology, mechanism of action subsection.
- b. Statement regarding source of endogenous erythropoietin production deleted as irrelevant to the manufactured drug.

12. Clinical Pharmacology

- a. Section on Mechanism of action: The majority of this section was deleted because it is either covered in other sections (PD or PK subsections of clinical pharmacology or Clinical Studies subsections).
- b. Section on PD: Deleted redundant information in second sentence, first paragraph. FDA requests clarification of populations referenced in comment regarding failure to respond at doses of more than 300 U/kg three times per week.

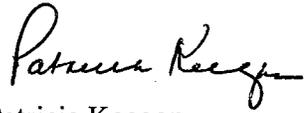
- c. Section on PK: deleted comparisons of PK in CRF and healthy subjects as irrelevant.
Re-worded comparisons of PK in CRF patients on and not on dialysis for clarity.
Deleted comparisons of PK by formulation as irrelevant.
- 13. Non-Clinical Toxicology**
- a. Section on Reproductive and Developmental 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.
- 14. Clinical Studies**
- a. In general, section revised to include appropriate clinical trial description in accordance with the Guidance for Industry document on this section of the label, including description of study population (demographics).
 - b. Data should be limited to primary efficacy endpoints and data used by FDA as primary support to expand labeling claims (e.g., information in HIV-infected patients regarding lack of impact on HIV or other infections and on leukopenia deleted as irrelevant to determination of efficacy). Similarly, information on rate of hemoglobin increase in patients with CRF deleted because this information was not primary basis establishing efficacy in support of approval.
 - c. Information on three-times-per-week dosing schedule in patients with anemia due to myelosuppressive chemotherapy deleted; use of this regimen is uncommon and the studies are less relevant in characterizing drug effects than the larger weekly dosing study which is retained in this section.
- 15. How Supplied and Handling Information**
- a. Information previously provided in dosage forms and strengths moved to this section.
- 16. Patient Counseling Information** Re-worded for ‘active voice’ and brevity.

Signature Page:



Kaushik Shastri, M.D.
Clinical Reviewer,
DBOP

Through:



Patricia Keegan,
Acting Team Leader,
DBOP

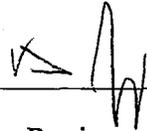
CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Yes	No	N/A	Comment
FORMAT/ORGANIZATION/LEGIBILITY				
1. On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	X			
2. Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
3. For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
4. Are all documents submitted in English, or are English translations provided when necessary?	X			
5. On its face, is the clinical section of the application legible so that substantive review can begin?	X			
LABELING				
6. Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56 ¹ and 201.57, current divisional and Center policies, and the design of the development package?			X	
SUMMARIES				
7. Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?			X	
8. Has the applicant submitted the integrated summary of safety (ISS)?			X	
9. Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
10. Has the applicant submitted a benefit-risk analysis for the product?		X		
DOSE				
11. If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?			X	
EFFICACY				
12. On its face, do there appear to be the requisite number of adequate and well controlled studies in the application?	X			
13. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
SAFETY				
14. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
15. Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
16. Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?		X		

¹ http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html

OTHER STUDIES			
17. Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?	X		
18. For an Rx-to-OTC switch application, are the necessary special OTC studies included (e.g., labeling comprehension)?			X
PEDIATRIC USE			
19. Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X
ABUSE LIABILITY			
20. If relevant, has the applicant submitted information to assess the abuse liability of the product?			X
FOREIGN STUDIES			
21. Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X	
DATASETS			
22. Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X		
23. Has the applicant submitted datasets in the the format agreed to previously by the Division?	X		
24. Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X		
25. Are all datasets to support the critical safety analyses available and complete?	X		
26. For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints?	X		
CASE REPORT FORMS			
27. Has the applicant submitted all required Case Report forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X		
28. Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X		
FINANCIAL DISCLOSURE			
29. Has the applicant submitted the required Financial Disclosure information?		X	
GOOD CLINICAL PRACTICE			
30. Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X
CONCLUSION			
31. From a clinical perspective, is this application fileable? If "no", please state why it is not?	X		

Signature Page

 4/22/08

Reviewer Signature/Date

Concurrence by Team Leader: Signature/Date