CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103951Orig1s5173

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

PATIENT LABELING REVIEW

Date:	April 20, 2011
To:	Patricia Keegan, MD, Director **Division of Biologic Oncology Products (DBOP)**
Through:	LaShawn Griffiths, RN, MSHS-PH, BSN Acting Team Leader, Patient Labeling Reviewer **Division of Risk Management (DRISK)** 4/20/11 Barbara Fuller, RN, MSN, CWOCN Barbara Fuller 4/20/11 Acting Team Leader, Patient Labeling Reviewer **Division of Risk Management**
From:	Sharon R. Mills, BSN, RN, CCRP Sharon R. Mills 4/20/11 Senior Patient Labeling Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling (Medication Guide and Patient Instructions for Use)
Drug Name (established name):	Epogen/Procrit (epoetin alfa) Aranesp (darbepoetin alfa)
Dosage Form and Route:	injection
Application Type/Number:	BLA 103234/5166 BLA 103951/5173
Applicant:	Amgen
OSE RCM #:	2009-2286

1 INTRODUCTION

This review is written in response to a request by the Division of Biologic Oncology Products (DBOP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) and Patient Instructions for Use (IFU) for Epogen/Procrit (epoetin alfa), BLA 103234/5166 and Aranesp (darbepoetin alfa) BLA 103951/5173. The purpose of the Applicant's submission is to submit PLR supplements for Epogen/Procrit and Aranesp (darbepoetin alfa) in response to the Agency's April 27, 2010 Complete Response (CR) letter, and to modify the Erythropoiesis Stimulating Agents (ESAs) Risk Evaluation and Mitigation Strategy (REMS).

The REMS is under review by DRISK and will be provided to DBOP under separate cover.

2 MATERIAL REVIEWED

- Draft Epogen/Procrit (epoetin alfa) Medication Guide (MG), Instructions for Use (IFU) for received on March 23, 2011 and sent to DRISK on March 24, 2011
- Draft Aranesp (darbepoetin alfa) Medication Guide (MG), IFUs: Single-Dose Vial, Single-Dose Prefilled Syringe (SingleJect), and Single-Use Prefilled SureClick Autoinjector, received on March 23, 2011 and sent to DRISK on March 24, 2011
- Draft Epogen/Procrit prescribing information (PI) received March 23, 2011 and sent to DRISK on March 24, 2011.
- Draft Aranesp (darbepoetin alfa) prescribing information (PI) received March 23, 2011, and sent to DRISK on March 24, 2011.

3 REVIEW METHODS

In our review of the MGs, IFUs we have:

- performed side-by-side reviews of the Applicant's submitted MGs and IFUs for Epogen/Procrit (epoetin alfa) and Aranesp (darbepoetin alfa) with the Agency revised MGs and IFUs dated March 8, 2011, and sent to Amgen on March 16, 2011.
- performed a complete review of the Aranesp Single-Use Prefilled SureClick Autoinjector IFU. In the Complete Response letter dated April 27, 2010, DBOP requested that the Applicant revise the format of this device to be consistent with the Single-Dose Vial, Single-Dose Prefilled Syringe (SingleJect) IFUs.
- ensured that the Epogen/Procrit (epoetin alfa) and Aranesp (darbepoetin alfa) MGs and IFUs are consistent with the prescribing information (PI) sent to Amgen on March 16, 2011.
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG, IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

4 CONCLUSIONS

The Epogen/Procrit (epoetin alfa) and Aranesp (darbepoetin alfa) MGs and IFUs are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the Epogen/Procrit (epoetin alfa) and Aranesp (darbepoetin alfa) MGs and IFUs are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MGs or IFUs.

Please let us know if you have any questions.

132 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Cc List:

DBOP:
Patricia Keegan
Jeff Summers
Mona Patel

OSE:
Claudia Karwoski
Mary Willy
LaShawn Griffiths
Barbara Fuller
Mary Dempsey
Sue Kang

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Federal Research Center
Tel. 301-796-4242

Memorandum

PROJECT MANAGER'S REVIEW

Application Number: STN ~~103234/5166~~ 103951/5173

Name of Drug: Aranesp® (darbepoetin alfa)

Sponsor: Amgen Manufacturing Limited

Material Reviewed: Aranesp® (darbepoetin alfa) Highlights and Prescribing Information

OBP Receipt Date: January 4, 2010

Background:

Amgen has submitted a supplement to BLA 103951 to incorporate the Physician's Labeling Rule (PLR) conversion of the package insert for Aranesp® (darbepoetin alfa).

Label Reviewed:

Aranesp® (darbepoetin alfa) Highlights and Prescribing Information-

- Product Title
- Dosage Forms and Strengths
- Dosage and Administration
- Description
- Manufacturer information

Review

The changes to the prescribing information label for Aranesp® (darbepoetin alfa) were reviewed and found to conform to most of the regulations under 21 CFR 610 –Subpart G and 21 CFR 201.57. Please see the Conclusions section for comments.

Conclusions:

The following deficiencies were noted on the initial review of the Prescribing Information labeling for Aranesp® (darbepoetin alfa).

1. HIGHLIGHTS OF PRESCRIBING INFORMATION
   a. Please revise the Product title line to include the dosage form and route of administration below the presentation of the Trade name and proper name. The dosage form as defined by the United States Pharmacopeia should be "injection" and the route of administration is "for intravenous or subcutaneous use".

2. Full Prescribing Information
   a. Dosage and Administration
      i. Please revise the statement "Do not shake" to [redacted] (b) (4)
      ii. Please revise the statement currently located in section 2.4, [redacted] (b) (4)

   b. DESCRIPTION
      i. Per USPC Official 12/1/09-5/1/10, USP 32/NF27, <1091> Labeling of Inactive Ingredients, please list the names of all inactive ingredients in alphabetical order followed by the amount. Suggested format: inactive ingredient (amount)

   b. HOW SUPPLIED/STORAGE AND HANDLING
      i. Please revise the statement, [redacted] (b) (4)
      ii. Please add the statement, [redacted] (b) (4)

3/30/10

Kimberly Rains, Pharm.D.
Regulatory Project Manager
CDER/OPS/OBP/IOD

Ingrid Markovic, Ph.D.
Product Reviewer
CDER/OPS/OBP/DTP

Comments/Concurrence:

Barry Cherney, Ph. D.
Deputy Director
Division of Therapeutic Proteins
CDER/OPS/OBP

FILE AMENDMENT

Amendment Date: 02/02/2010 **PM:** Ebla Ali Ibrahim

TO BLA: 103951

Submission Date: 10/23/2009

FDA Received Date: 10/23/2009

SDN / SN: BLA 103951/5173

eCTD number: Sequence No. 0309

Network path in edr: <\\cbsap58\M\eCTD_Submissions\STN103951\103951.enx>

FROM: Saleh Ayache, MD, Medical Reviewer; Division of Medical Imaging and Hematology Products 3/10/2010

SUBJECT: Review of Aranesp PLR prior approval supplement re-submission in response to the CR letter from FDA

Via: Robert Kane, MD, team leader, DDOP, OODP TC Kane 3/10/2010

BACKGROUND: On October 23, 2009, Amgen resubmitted a revised Prior Approval Supplement for the physician labeling rule (PLR) conversion for Aranesp, in response to FDA's Complete Response Letter dated October 24, 2008. The original submission was reviewed by Dr. Minh-Ha Tran from DMIHP dated 10-20-2008.

ISSUE:

Amgen made the following changes to the 2008 FDA proposed label of Aranesp:

(b) (4)

(b) (4)

- **Adverse Reactions**: No changes
- **Use in Specific Populations**: *(see PHMT review)*

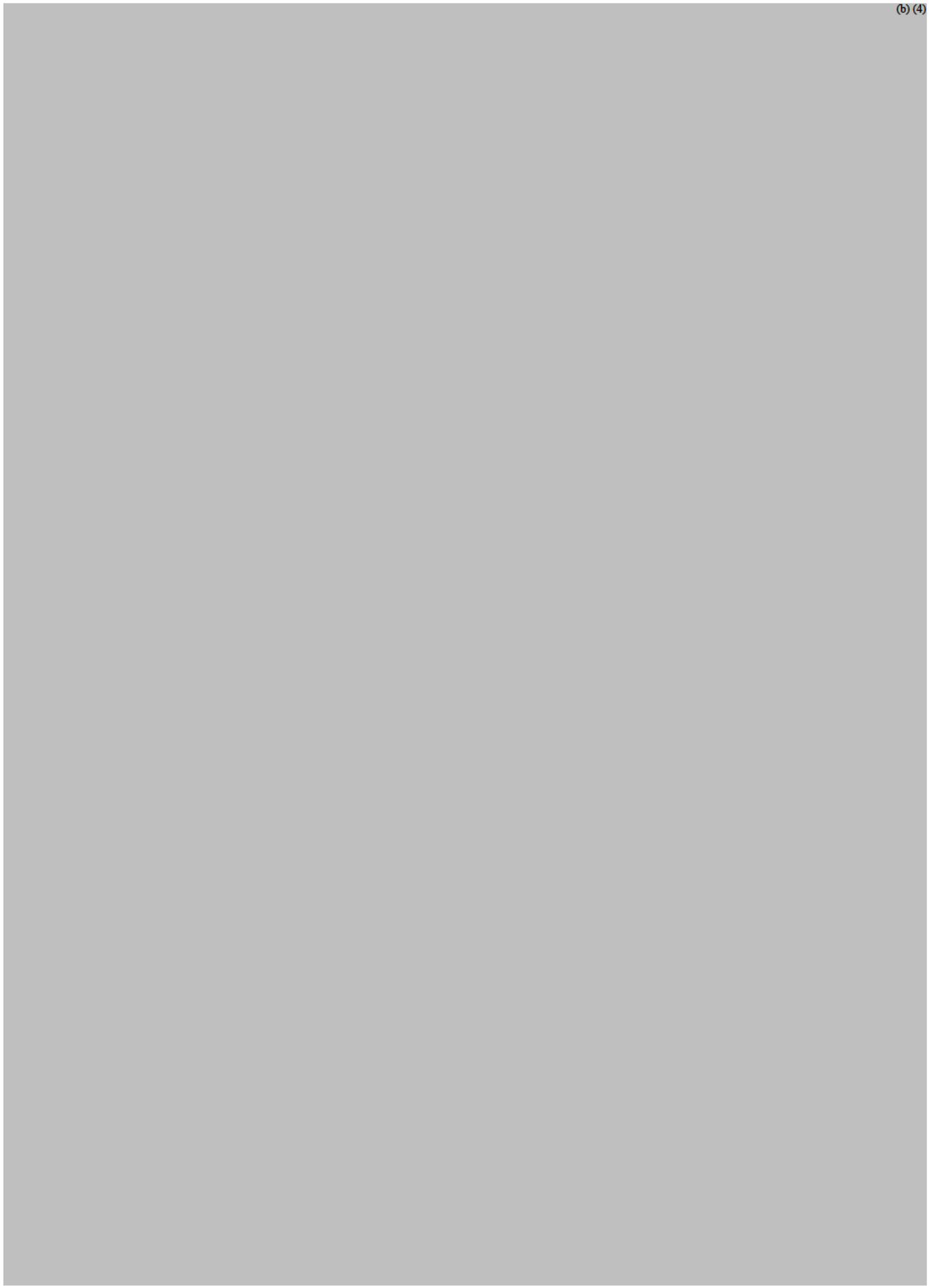
II. Boxed Warning: See comments above under the Box Warning in highlight sections.

III. Label Sections:

(b) (4)

2.3. Preparation and Administration: *(see CMC comments)*

3. DOSAGE FORMS AND STRENGTHS:
(see CMC comments).


(b) (4)

6.3. Immunogenicity: (See Clinical Pharmacology review).

7. DRUG INTERACTIONS:
(See Clinical Pharmacology review).

8. USE IN SPECIFIC POPULATIONS:
8.1. Pregnancy: *(see PMHT review).*
8.2.
8.3. Nursing Mothers: *(see PMHT review).*

8.4. Pediatric Use: *(see PMHT review).*

(b) (4)

[redacted]

11. DESCRIPTION:
(See CMC comments)

12. CLINICAL PHARMACOLOGY:
12.1. Mechanism of Action: *(see Clinical Pharmacology Review)*
12.2. Pharmacodynamics: *(see Clinical Pharmacology Review)*
12.3. Pharmacokinetics: *(see Clinical Pharmacology Review)*

13. NONCLINICAL TOXICOLOGY:
13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility: (*see Pharm. Tox. Review)*
13.2.
13.3. Reproductive and Developmental Toxicology: (*see Pharm. Tox. Review)*

14. CLINICAL STUDIES:

(b) (4)

[redacted]

14.2. Cancer Patients Receiving Chemotherapy: *(see DBOP Review).*

15.
16. HOW SUPPLIED/STORAGE AND HANDLING:
(see CMC Review)

ACTIONS RECOMMENDED: The following recommendations should be conveyed to the sponsor:

1. We agree to the addition of stoke in the box warning and a summary of the treat study under section
2. The changes from (b) (4) through out the box warning and in section (5.1) are not acceptable (b) (4)
3. (b) (4)
4.
5.
6. Add that PRCA that begins after treatment with Aranesp or other erythropoietin protein drugs as contraindication for use of Aranesp in section (4) of the label.
7. (b) (4)
8.
9.
10. Add section (5.4) Lack or Loss of Hemoglobin Response to Aranesp.
11. (b) (4)
12.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	March 9, 2010
To:	Patricia Keegan, M.D., Director **Division of Biologic Oncology Products (DBOP)**
Through:	Mary Willy, Ph D, Deputy Director Mary Willy 3/9/2010 **Division of Risk Management (DRISK)**
	Sharon R. Mills, BSN, RN, CCRP Sharon R. Mills 3/9/2010 Senior Patient Labeling Reviewer, Acting Team Leader **Division of Risk Management**
From:	Melissa Hulett MSBA, BSN, RN Melissa Hulett 3/9/2010 Patient Labeling Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling (Medication Guide and Instructions for Use)
Drug Name(s):	Aranesp (darbepoetin alfa)
Application Type/Number:	BLA 103951/5173
Submission Date:	October 26, 2009
Applicant/sponsor:	Amgen Pharmaceuticals
OSE RCM #:	2009-2286

1 INTRODUCTION

Amgen Pharmaceuticals resubmitted a Prior Approval Supplement on October 23, 2009 in response to FDA's Complete Response Letter dated October 24, 2008. The submission addresses the PLR conversion of supplement BL STN 103951/5173.

This review is written in response to a request by the Division of Biologic Oncology Products (DBOP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) and three Instructions for Use for Aranesp (darbepoetin alfa).

We plan to meet with DBOP on Tuesday, March 9, 2010 to discuss this review prior to sending to the Applicant.

2 MATERIAL REVIEWED

- Draft Aranesp (darbepoetin alfa) Prescribing Information (PI) submitted October 26, 2009, and revised by the Review Division throughout the current review cycle and provided to DRISK on February 22, 2010.
- Draft Aranesp (darbepoetin alfa) Medication Guide (MG) submitted on October 26, 2009, revised by the review division throughout the review cycle and provided to DRISK on February 22, 2010.
- Draft Aranesp (darbepoetin alfa) three Patient Instructions for Use (IFU)-Single-Use Prefilled SureClick™ Autoinjector, Single-Dose Prefilled Syringe (SingleJect®), and Single-Dose Vial, submitted on October 26, 2009 and provided to DRISK on February 22, 2010.

3 RESULTS OF REVIEW

In our review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- rearranged information due to conversion of the PI to PLR format
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated MG and IFUs are appended to this memo. Any additional revisions to the PI should be reflected in the MG.

Please let us know if you have any questions.

64 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

CC list:

DBOP:
Patricia Keegan
Jeff Summers
Mona Patel

DMIHP:
Dwayne Rieves

OSE:
Mary Willy
Claudia Karwoski
Melissa Hulett
Sharon Mills
Mary Dempsey
LaShawn Griffiths
Sarah Simon

DDMAC:
Cynthia Collins
Wayne Amchin

Division of Drug Marketing, Advertising, and Communications

Internal Consult

****Pre-decisional Agency Information****

To: Mona Patel, Pharm.D., Regulatory Project Manager
Division of Biologic Oncology Products (DBOP)
Office of Oncology Drug Products

From: Carole C. Broadnax, R.Ph., Pharm.D. /s/ Broadnax 3/4/10
Division of Drug Marketing, Advertising and Communications (DDMAC)

Date: March 4, 2010

Re: **Aranesp (darbepoetin alfa)**
STN BL 103951/5173
Comments on draft product labeling

In response to DBOP's Request for Consultation dated November 25, 2009, DDMAC has reviewed the revised draft product labeling (PI) sent by electronic mail from DBOP on February 23, 2010, for Aranesp.

Reference is also made to DDMAC's January 14, 2010, Internal Consult Memorandum where DDMAC provided comments on a previous version of this draft PI that DBOP sent by electronic mail on January 11, 2010.

This draft product labeling converts the Aranesp PI into the Physician Labeling Rule format. The draft labeling also includes TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy) study data.

These comments are limited to those sections of the draft PI that DBOP has responsibility for review based on the plan discussed at the pre-Mid-Cycle meeting on January 7, 2010.

We offer the following comments:

DDMAC does not have comments at this time on those sections of the revised draft PI that DBOP has responsibility for review.

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

******Pre-decisional Agency Information******

Memorandum

Date: March 4, 2010

To: Mona Patel, PharmD – Regulatory Project Manager
Division of Biologic Oncology Products (DBOP)

From: Michelle Safarik, PA-C – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Michelle Safarik 3/4/10

Subject: Aranesp® (darbepoetin alfa) (Aranesp)
BLA 103951
DDMAC comments on revised proposed product labeling (PI)

DDMAC has reviewed the proposed PI for Aranesp dated February 22, 2010, and submitted for consult on February 23, 2010. Our comments are based on the most version of the proposed PI sent via e-mail from DBOP on February 23, 2010. This is the version that was sent to Amgen on February 22, 2010.

DDMAC acknowledges that the proposed PI converts the existing Aranesp PI into Physician Labeling Rule (PLR) format. Thus, we may commenting on language in the proposed PI that is already approved. In addition, the proposed PI includes data from the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) study.

Please note these comments are limited to those sections of the proposed PI in which the Division of Medical Imaging and Hematology's (DMIHP) is taking the lead. (Reference is made to the pre-midcycle meeting on January 7, 2010, where it was decided which group would take the lead on which sections of the proposed PI.) We offer the following comments.

Full Prescribing Information

Clinical Pharmacology

Pharmacokinetics – Adult CRF Patients

1. "Following SC administration of Aranesp to CRF patients…absorption was slow and Cmax occurred at 48 hours (range: 12 to 72 hours)." (emphasis added)

   "Slow" is promotional in tone. We recommend deleting, as context (i.e., 48 hours, range: 12 to 72 hours) is provided later in the sentence.

Patient Counseling Information

1. We recommend that the prescriber also counsel patients on serious allergic reactions (and possible signs and symptoms of serious allergic reactions) as well as the most common adverse reactions for consistency with the Warnings and Precautions and Adverse Reactions sections of the proposed PI.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY INFORMATION****

Date: March 4, 2010

To: Patricia Keegan, M.D.
Supervisory Medical Officer
Division of Biologic Oncology Products (DBOP)

Kaushikkumar Shastri, M.D.
Medical Officer
DBOP

Mona Patel, Pharm.D.
Regulatory Project Manager
DBOP

From: Cynthia Collins, Ph.D. 03-04-2010.
Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Re: **BLA 103951/5173: ARANESP (darbepoetin alfa for Injection)**
DDMAC label consult response Aranesp Medication Guide

Background:

DDMAC has reviewed the following draft Medication Guide (MG) for Aranesp:

- "FDA Proposed Changes Medguide Aranesp Clean 2 22 2010"
- revised February 22, 2010
- accessed from February 23, 2010, e-mail from Mona Patel

DDMAC comments on the draft prescribing information (PI) for Aranesp will be provided under separate cover.

We offer the following comments on the draft Medication Guide:

1. Under "**Patients with cancer:**" the MG states (emphasis added):

(b) (4)

2. Under "**What are the possible side effects of Aranesp?**" the MG states (underline emphasis added):

(b) (4)

(b) (4)

General Comments

1. In our review, we noted the following typos in the draft MG:

    - Page 3: The phone number for the pregnancy registry says "1-800-772-6436 fl-800-77-AMGEN)."
    - Page 4: The abdominal pain common side effect bullet says "Abominal pain in cancer patients"

DDMAC appreciates the opportunity to provide comments on these materials. If you have any questions, please contact:

- Cynthia Collins
  (301) 796-4284, or cynthia.collins@fda.hhs.gov

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
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Maternal Health Team (MHT) Review

Date: February 26, 2010 **Date Consulted:** November 25, 2009

From: Richardae Araojo, Pharm.D. Richardae Araojo 3/2/2010
Regulatory Reviewer
Pediatric and Maternal Health Staff

Through: Karen Feibus, MD
Medical Team Leader, Maternal Health Team 3/2/10
Pediatric and Maternal Health Staff

Lisa Mathis, MD 3/2/2010
Associate Director, Office of New Drugs
Pediatric and Maternal Health Staff

To: Division of Medical Imaging and Hematology Products (DMIHP)

Drug: Aranesp (darbepoetin alfa); BLA 103951/5173/5010

Subject: Pregnancy and Lactation Labeling

Materials Reviewed: Pregnancy and Nursing Mother's subsections of proposed labeling.

Consult Question: Please review the sponsor's proposed labeling in response to the FDA's complete response letter.

BACKGROUND

On December 20, 2007, Amgen submitted a prior approval supplement to the Division of Medical Imaging and Hematology Products (DMIHP) for Aranesp (darbepoetin alfa). Aranesp is an erythropoiesis-stimulating agent (ESA) indicated for the treatment of anemia due to chronic renal failure and myelosuppressive cancer chemotherapy. The December 2007 supplement proposed revisions to Aranesp prescribing information and reformatted the labeling according to the Physician's Labeling Rule (PLR). On October 24, 2008, the FDA issued a Complete Response letter that included the Division's proposed labeling. On October 23, 2009, Amgen submitted a response to the FDA's Complete Response letter. DMIHP consulted the Maternal Health Team (MHT) and requested review of the Pregnancy and Nursing Mothers subsections of the sponsor's proposed label.

This review will provide the MHT's recommended revisions to the sponsor's proposed labeling related to pregnancy and lactation.

REVIEW OF SUMBMITTED MATERIAL

Table 1 below presents the current approved labeling for Aranesp, FDA labeling issued in the Complete Response letter dated October 24, 2008, and the sponsor's proposed labeling in response to the FDA's Complete Response letter. In addition, Table 1 provides the MHT reviewer's comments on the sponsor's proposed labeling.

Table 1. Aranesp (darbepoetin alfa) Labeling			
Current Approved Labeling	**Agency Labeling in Complete Response Letter dated October 24, 2008**	**Sponsor's Proposal**	**MHT Reviewer Comments**
Label not in PLR format.	[redacted] (b) (4)	[redacted]	• Agree with sponsor's proposal. • Note to Division: MHT received information Amgen submitted regarding their Pregnancy Surveillance Program (submitted to a different application).
Pregnancy Category C When Aranesp was administered intravenously to rats and rabbits during gestation, no evidence of a direct embryotoxic, fetotoxic, or teratogenic outcome was observed at doses up to 20 mcg/kg/day. The only adverse effect observed was a slight reduction in fetal weight, which occurred at doses causing exaggerated pharmacological effects in the dams (1 mcg/kg/day and higher). No deleterious effects on uterine implantation were seen in either species. No significant placental transfer of Aranesp was observed in rats. An increase in post implantation fetal loss was	[redacted]	[redacted]	• Label should include a range for human equivalent exposures that correlate with animal doses presented in this section. • Note to Division: Periodic Safety Update Report (PSUR) dated December 16, 2009 reported 59 pregnancy exposures and outcomes for 37 exposures. There were no reported exposures during lactation.

observed in studies assessing fertility (see **PRECAUTIONS: Carcinogenesis, Mutagenesis, and Impairment of Fertility: Impairment of Fertility**). Intravenous injection of Aranesp to female rats every other day from day 6 of gestation through day 23 of lactation at doses of 2.5 mcg/kg/dose and higher resulted in offspring (F1 generation) with decreased body weights, which correlated with a low incidence of deaths, as well as delayed eye opening and delayed preputial separation. No adverse effects were seen in the F2 offspring. There are no adequate and well-controlled studies in pregnant women. Aranesp should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.	(b) (4)		
Nursing Mothers It is not known whether Aranesp is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Aranesp is administered to a nursing woman.			• Language should be revised to include required regulatory language [21CFR 201.57], "caution should be exercised when Aranesp is administered to a nursing woman."
Medication Guide **What should I tell my**			No comments.

healthcare provider before taking Aranesp? Aranesp may not be right for you. **Tell your healthcare provider about all your health conditions,** including if you: • Are pregnant or planning to become pregnant. It is not known if Aranesp will harm your unborn baby. • Are breast-feeding or planning to breast-feed. It is not known if Aranesp passes into breast milk.			

DISCUSSION AND CONCLUSIONS

For this review, the MHT made revisions to sections of the division's most recent revised version of the sponsor's proposed Aranesp labeling related to pregnancy and lactation. In addition, the MHT reviewer noted that the December 2009 PSUR provides a summary of 59 Aranesp pregnancy exposures and no reported exposures during lactation.

RECOMMENDATIONS

1. The MHT recommends that the Division issue a labeling supplement request letter to the sponsor requesting inclusion of relevant human data (including published data) on darbepoetin exposure during pregnancy.

2. The MHT recommends the following language for the Highlights, Pregnancy, and Nursing Mothers sections of Aranesp labeling.

HIGHLIGHTS OF PRESCRIBING INFORMATION
----------USE IN SPECIFIC POPULATIONS----------

(b) (4)

8.1 Pregnancy
Pregnancy Category C

(b) (4)

In a peri/postnatal development study, pregnant female rats received Aranesp IV every other day from implantation throughout pregnancy and lactation. The lowest dose

received, 0.5 mcg/kg, did not cause fetal toxicity; this dose is approximately equivalent to the clinical recommended starting dose. At maternal doses of 2.5 mcg/kg and higher, pups had decreased fetal body weights, which correlated with a slight increase in the incidence of fetal deaths, as well as delayed eye opening and delayed preputial separation [*see Nonclinical Toxicology (13.3)*].

Women who become pregnant during Aranesp treatment are encouraged to enroll in Amgen's Pregnancy Surveillance Program. Patients or their physicians should call 1-800-772-6436 (1-800-77-AMGEN) to enroll.

8.3 Nursing Mothers

It is not known whether Aranesp is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Aranesp is administered to a nursing woman.

MEMORANDUM

To: **Mona Patel, PharmD**
Division of Biologic Oncology Products

From: **Iris Masucci, PharmD, BCPS**
Division of Drug Marketing, Advertising, and Communications
for Study Endpoints and Label Development (SEALD) Team, OND

Date: **February 18, 2010**

Re: **Comments on draft labeling for Aranesp (darbepoetin alfa)**
STN 103951/5173

We have reviewed the proposed label for the Complete Response resubmissions for Aranesp (FDA version dated 2/18/10) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the Division after a full review of the submitted data.

Please see attached label for recommended changes. Note that many other labeling recommendations were made verbally at team labeling meetings and were incorporated into the labeling prior to this version.

21 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9744

Pediatric and Maternal Health Staff Review

Date: February 1, 2010 **Date Consulted:** November 25, 2010

From: Jeanine Best, MSN, RN, PNP, Clinical Analyst
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff (PMHS)

Through: Hari Cheryl Sachs, MD, Lead Medical Officer
Lisa Mathis, MD, OND Associate Director
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff (PMHS)

To: Division of Medical Imaging and Hematology Products (DMIHP) and Division of Biological Oncology Products (DBOP)

Drug: Aranesp (darbepoetin alfa) for injection, BLA 103951/5173/5010

Subject: Labeling Review

Materials Reviewed:

- Sponsor Labeling submission dated December 20, 2007
- Sponsor Labeling submission dated October 23, 2009, revised labeling dated January 26, 2010
- PMHS/Pediatric Review of proposed pediatric oncology studies for July 16, 2008, Industry meeting
- PMHS/Pediatric Memorandum dated January 26, 2009 regarding request for full waiver of pediatric oncology studies

Consult Question: Review pediatric use information in labeling for PLR conversion of approved labeling.

Note: PMHS – Pediatric Team was not consulted on the initial submission (December 20, 2007) of this supplemental application.

INTRODUCTION

Aranesp® (darbepoetin alfa) for injection was approved September 17, 2001, for the treatment of anemia associated with chronic renal failure in adults, including patients on dialysis and patients not on dialysis. Darbepoetin alfa is an erythropoiesis stimulating protein closely related to erythropoietin that is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. Darbepoetin alfa has an approximately 3-fold longer terminal half-life than Epoetin alfa when administered by either the intravenous (IV) or subcutaneous (SC) route.

Additional indications approved for Aranesp® in adults include:

- for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy (July 19, 2002)

Pediatric indication:

- in the initial treatment of anemic pediatric patients with CRF or in the transition from another erythropoietin to Aranesp® in pediatric CRF patients less than 1 year of age (December 5, 2005)

Amgen submitted a Prior Approval Labeling Supplement for Aranesp® on December 20, 2007, in response to a May 31, 2007, Supplement Request Letter, in which FDA requested revised prescribing information to address recommendations made at the May 10, 2007, Oncology Drug Advisory Committee meeting, and to reformat the labeling according to the Physician's Labeling Rule (PLR). Data was submitted to support proposed revisions to the hemoglobin initiation level, the maximum hemoglobin level, and the discontinuation of ESA therapy post-chemotherapy. FDA issued a Complete Response Letter on October 24, 2008, and Amgen submitted their resubmission in response to the Complete Response Letter on October 23, 2009. The Pediatric Team of the Pediatric and Maternal Health Staff was consulted to review the pediatric use information in the Aranesp® labeling.

BACKGROUND

As noted above, Aranesp® (darbepoetin alfa) for injection was approved September 17, 2001. Erythropoiesis-stimulating agents have been associated with increased mortality, serious cardiovascular and thromboembolic events, increased risk of tumor progression or recurrence, and antibody-mediated pure red cell aplasia. Due to ESA safety concerns, multiple communications and labeling changes have occurred over the past several years. The following communications have been disseminated by FDA and the drug Sponsor (Amgen) to advise of safety concerns and safety-related labeling revisions with ESA products:

FDA Communications:

- November 16, 2006: FDA Public Health Advisory and Information for Healthcare Professionals: to advise of a newly published clinical study showing that patients treated with an erythropoiesis-stimulating agent (ESA) and dosed to a target hemoglobin concentration of 13.5 g/dL are at a significantly increased risk for serious and life threatening cardiovascular complications, as compared to use of the ESA to target a hemoglobin concentration of 11.3 g/dL,

- March 9, 2007: FDA Public Health Advisory, Information for Healthcare Professionals and Questions and Answers to inform of recent reports of studies with erythropoiesis-stimulating agents (ESAs) that have shown a higher chance of serious and life-threatening side effects and greater number of deaths in patients treated with these agents. ESAs stimulate the bone marrow to make more red blood cells and are FDA approved for use in reducing the need for blood transfusions in patients with chronic kidney failure, patients with cancer on chemotherapy, patients scheduled for major surgery (except heart surgery) and patients with HIV that are using AZT. Because all ESAs work the same way, the findings from these studies apply to all ESAs; the FDA is re-evaluating the safe use of this drug class.

- June 26, 2006: Statement from OND Director on ESA safety before the Committee on Ways and Means Subcommittee on Health, U.S. House of Representatives

- November 8, 2007: FDA Public Health Advisory and Questions and Answers informing that FDA has approved revised labeling for the ESAs that clarifies how to safely and effectively use these products and to strengthen the information about risks from using ESAs.

- January 3, 2008: FDA Communication about an ongoing safety review and Information for Healthcare Professionals informing with the findings from two additional clinical studies (PREPARE and GOG-191 studies) showing an increase in mortality and shorter time to tumor progression in patients with cancer receiving an ESA. This new information further underscores the safety concerns regarding the use of ESAs in patients with cancer addressed in previous communications.

- October 1, 2008: Information for Healthcare Professional advising of Labeling changes as a follow up to the 1/3/08 communication.

Sponsor Communications:

- March 7, 2008: Dear Healthcare Professional Letter, Subject: Additional trials showing increased mortality and/or tumor progression.
- August 7, 2008: Dear Healthcare Professional Letter, Subject: Strengthened oncology safety information, New Medication Guide and Patient Instructions for Use.
- November 8, 2008: Dear Healthcare Professional Letter, Subject: Increased mortality, serious Cardiovascular and Thromboembolic events and tumor progression.
- April 8, 2009: Dear Healthcare Professional Letter, Subject: Reports of antibody-mediated pure red cell aplasia and transfusion dependent anemia in patients with hepatitits C virus treated with ribaviron and interferon or pegylated interferon and an ESA concurrently.

Required pediatric oncology studies under the Pediatric Research and Equity Act of 2007 were waived because necessary studies are impossible or highly impracticable.

REVIEW OF LABELING AND PMHS/PEDIATRICS RECOMMENDATIONS
Proposed Aranesp® Labeling dated January 26, 2010

PMHS/Pediatrics recommended labeling revisions are noted in reviewer comments.

The following sections of Aranesp® labeling include pediatric-specific use information.

Highlights of Prescribing Information

----------USE IN SPECIFIC POPULATIONS----------

(b) (4)

Reviewer Comment: Highlights of Prescribing Information is a new section for labeling in the PLR format. Per 21 CFR 201.57(a)(13), The Use in Specific Populations/Pediatric Use should contain a concise summary of the information presented in subsection 8.4 Pediatric Use. Revise statement to:

(b) (4)

2 DOSING AND ADMINISTRATION
2.2 Chronic Renal Failure Patients

Conversion from Epoetin alfa to Aranesp

Aranesp should be administered less frequently than epoetin alfa.

- Administer Aranesp once weekly in patients who were receiving epoetin alfa 2 to 3 times weekly.
- Administer Aranesp once every 2 weeks in patients who were receiving epoetin alfa once weekly.

Estimate the starting weekly dose of Aranesp for adults and pediatric patients on the basis of the weekly epoetin alfa dose at the time of substitution (see Table 1). Maintain the route of administration (intravenous or subcutaneous injection).

Table 1. Estimated Aranesp Starting Doses (mcg/week) Based on Previous Epoetin alfa Dose (Units/week)

Previous Weekly Epoetin alfa Dose (Units/week)	Weekly Aranesp Dose (mcg/week)	
	Adult	Pediatric
< 1,500	6.25	*
1,500 to 2,499	6.25	6.25
2,500 to 4,999	12.5	10
5,000 to 10,999	25	20
11,000 to 17,999	40	40
18,000 to 33,999	60	60
34,000 to 89,999	100	100
≥ 90,000	200	200

*For pediatric patients receiving a weekly epoetin alfa dose of < 1,500 Units/week, the available data are insufficient to determine an Aranesp conversion dose.

Reviewer Comment: The language is identical to the current approved labeling language with a minor edit. PMHS/Pediatrics has no revisions or edits for this section.

6 ADVERSE REACTIONS
6.1 Clinical Trial Experience
Chronic Renal Failure Patients

Pediatric Patients

Aranesp was administered to 81 pediatric CRF patients who had stable hemoglobin concentrations while previously receiving epoetin alfa [*see Clinical Studies (14.1)*]. In this study, the most frequently reported serious adverse reactions with Aranesp were hypertension and convulsions. The most commonly reported adverse reactions were hypertension, injection site pain, rash, and convulsions. Aranesp administration was discontinued because of injection site pain in 2 patients and moderate hypertension in a third patient.

Studies have not evaluated the effects of Aranesp when administered to pediatric patients as the initial treatment for the anemia associated with CRF.

Reviewer Comment: The most commonly reported adverse events in pediatric CFR patients were updated in a previous version of labeling. No further revisions were proposed with this submission. PMHS/Pediatrics has no revisions or edits for this section.

8 USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use

Pediatric CRF Patients

Aranesp safety and efficacy were similar between adults and pediatric patients with CRF

who were over 1 year of age when patients were transitioned from treatment with epoetin alfa to Aranesp [*see Clinical Pharmacology (12.3)* and *Clinical Studies (14.1)*]. Aranesp safety and efficacy have not been established in the initial treatment of anemic pediatric patients with CRF or in the transition from another erythropoietin to Aranesp in pediatric CRF patients less than 1 year of age.

Pediatric Cancer Patients

The safety and efficacy of Aranesp in pediatric cancer patients have not been established.

Reviewer Comment: Language is identical to the current approved labeling language. PMHS/Pediatrics has no revisions or edits to this section.

12 CLINICAL PHARMACOLOGY
12.3 Pharmacokinetics

Pediatric Patients

Aranesp pharmacokinetics were studied in 12 pediatric CRF patients (age 3 to 16 years) receiving or not receiving dialysis. Following a single intravenous or subcutaneous Aranesp dose, Cmax and half-life were similar to those obtained in adult CRF patients on dialysis. Following a single subcutaneous dose, the average bioavailability was 54% (range: 32% to 70%), which was higher than that obtained in adult CRF patients on dialysis.

Reviewer Comment: No proposed revisions to the current approved language. PMHS/Pediatrics has no revisions or edits.

14 CLINICAL STUDIES
14.1 Chronic Renal Failure Patients

(b) (4)

Conversion from Other Recombinant Erythropoietins

Two studies of adults (N5 and N6) and 1 study in pediatric patients (N7) were conducted in patients who had been receiving other recombinant erythropoietins for treatment of the anemia due to CRF. The studies compared the abilities of Aranesp and other erythropoietins to maintain hemoglobin concentrations within a study target range of 9 to 13 g/dL in adults and 10 to 12.5 g/dL in pediatric patients. (Note: The recommended hemoglobin target is lower than the target range of these studies [*see Dosage and Administration (2)*].) Patients who had been receiving stable doses of other recombinant erythropoietins were randomized to Aranesp or continued with their prior erythropoietin at the previous dose and schedule. For patients randomized to Aranesp, the initial weekly dose was determined on the basis of the previous total weekly dose of recombinant erythropoietin.

Pediatric Patients

Study N7 was an open-label, randomized study conducted in the United States in pediatric patients from 1 to 18 years of age with CRF receiving or not receiving dialysis. Eighty-one patients with hemoglobin concentrations that were stable on epoetin alfa received darbepoetin alfa (subcutaneously or intravenously), and 42 patients continued to receive epoetin alfa at the current dose, schedule, and route of administration. Patients received darbepoetin alfa once weekly if previously receiving epoetin alfa 2 or 3 times weekly or once every other week if previously receiving epoetin alfa weekly. A median weekly dose of 0.41 mcg/kg darbepoetin alfa (25th, 75th percentiles: 0.25, 0.82 mcg/kg) was required to maintain hemoglobin in the study target range.

Reviewer Comment: The pediatric study description was edited and revised to accurately describe the study. PMHS/Pediatrics defers review of the revised study description to DMIHP.

CONCLUSION

In summary PMHS recommends that the pediatric use information in Aranesp® labeling be revised as previously discussed in this review.

**Division of Drug Marketing,
Advertising, and Communications**

Internal Consult

****Pre-decisional Agency Information****

To: Mona Patel, Pharm.D., Regulatory Project Manager
Division of Biologic Oncology Products (DBOP)
Office of Oncology Drug Products

From: Carole C. Broadnax, R.Ph., Pharm.D. 1/14/10
Division of Drug Marketing, Advertising and Communications, CDER

Date: January 14, 2010

Re: **Aranesp (darbepoetin alfa)**
STN BL 103951/5173
Comments on draft product labeling

In response to DBOP's Request for Consultation dated November 25, 2009, DDMAC has reviewed the draft product labeling (PI) sent by electronic mail from DBOP on January 11, 2010, for Aranesp and offers the following comments.

This draft product labeling converts the Aranesp PI into the Physician Labeling Rule format. The draft labeling also includes TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy) study data.

These comments are limited to those sections of the draft PI that DBOP has responsibility for review based on the plan discussed at the pre-Mid-Cycle meeting on January 7, 2010.

Comments are included in the attached draft labeling.

21 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****Pre-decisional Agency Information****

Memorandum

Date: January 14, 2010

To: Mona Patel, PharmD – Regulatory Project Manager
Division of Biologic Oncology Products (DBOP)

From: Michelle Safarik, PA-C – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Michelle Safarik 1/14/10

Subject: Aranesp® (darbepoetin alfa) (Aranesp)
BLA 103951
DDMAC comments on proposed product labeling (PI)

DDMAC has reviewed the proposed PI for Aranesp dated October 26, 2009, and submitted for consult on November 25, 2009. Our comments are based on the most version of the proposed PI sent via e-mail from DBOP on January 11, 2010.

DDMAC acknowledges that the proposed PI converts the existing Aranesp PI into Physician Labeling Rule (PLR) format. Thus, we may commenting on language in the proposed PI that is already approved. In addition, the proposed PI includes data from the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) study.

Please note these comments are limited to those sections of the proposed PI in which the Division of Medical Imaging and Hematology's (DMIHP) is taking the lead. (Reference is made to the pre-midcycle meeting on January 7, 2010, where it was decided which group would take the lead on which sections of the proposed PI.) We offer the following comments.

Highlights

Warnings and Precautions

(b) (4)

We recommend specifying that Aranesp discontinuation be immediate as well as for consistency with the Warnings and Precautions section of the Full Prescribing Information.

Full Prescribing Information

Dosage and Administration

Chronic Renal Failure Patients – Dose Adjustment

1. (b) (4)

(b) (4)

Clinical Pharmacology

Pharmacokinetics – Adult Patients

(b) (4)

Patient Counseling Information

Information for Patients

(b) (4)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

******PRE-DECISIONAL AGENCY INFORMATION******

Date: January 14, 2010

To: Patricia Keegan, M.D.
Supervisory Medical Officer
Division of Biologic Oncology Products (DBOP)

Mona Patel, Pharm.D.
Regulatory Project Manager
DBOP

From: Cynthia Collins, Ph.D. 03-09-10
Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Re: DDMAC label consult response: CR resubmission, ESA Medication Guides
BLA 103951/5173: ARANESP (darbepoetin alfa for Injection)

Background:

DDMAC has reviewed the draft Medication Guides (MG) for the erythropoiesis-stimulating agent (ESA) Aranesp received on October 26, 2009, and located in the following electronic location:

- url: <\\cbsap58\M\eCTD_Submissions\STN103951\103951.enx>
- folder 0309, subfolder 1.14.1.3

DDMAC comments on the draft prescribing information (PI) for Aranesp will be provided under separate cover.

We offer the following comments on the draft Medication Guide:

1. Under "**Patients with cancer:**" the MG states:

2. Under "**Who should not take Aranesp?**" the MG states:

3. Under "**What should I tell my healthcare provider before taking Aranesp?**" the MG states:

- Are pregnant or planning to become pregnant. It is not known if Aranesp will harm your unborn baby.

Section 8.1 of the draft PI states that "Women who become pregnant during Aranesp treatment are encouraged to enroll in Amgen's Pregnancy Surveillance Program. Patients or their physicians should call 1-800-772-6436 (1-800-77-AMGEN) to enroll."

(emphasis added) *Would it be appropriate to include the information regarding Amgen's pregnancy patient registry in the MG?*

4. Under [redacted] (b) (4) the MG states (underline emphasis added):

[redacted] (b) (4)

DDMAC appreciates the opportunity to provide comments on these materials. If you have any questions, please contact:

- Cynthia Collins
  (301) 796-4284, or cynthia.collins@fda.hhs.gov

Division of Medical Imaging and Hematology Products

Sponsor	Amgen
Drug Name, Generic (Trade)	Darbepoetin alfa (Aranesp)
Indications	Anemia due to Chronic Renal Failure or Chemotherapy Treatment
Medical Officer	Minh-Ha Tran, D.O.
Acting Team Leader	Kassa Ayalew, M.D. 10/20/08
Division Director	Dwaine Rieves, M.D., Division Director
Application	BLA103951/5173, Darbepoetin alfa (Aranesp)
Submission Date	April 18 2008, SN 0208
Item	Medical Officer Review of PLR Submission

Table of Contents

1. Background

Amgen submitted a PAS (5173) for a proposed Physician Labeling Rule (PLR) supplement for Darbepoetin alfa (Aranesp) on April 18, 2008 (SN 0208) to the Division of Medical Imaging and Hematology Products (DMIHP).

FDA approved indications for Aranesp include:

1) Treatment of anemia due to chronic renal failure (CRF)
2) Treatment of anemia due to concomitant chemotherapy

2. Material Reviewed

Amgen submitted a Physician Labeling Rule (PLR) supplement to the Division of Medical Imaging and Hematology Products (DMIHP) on December 20, 2007 (SN 0096). The labeling submission included the following documents:

- Cover Letter
- Annotated Draft Labeling Text
- Proposed Physician Package Information
- clinical-overview-adr.pdf
  -containing justification for the submitted Adverse Reaction Tables and summarizing 5 randomized, active-controlled studies (970200, 970235, 980202, 980117, and 980211)
- pas-summary-clinical-safety.pdf
  -this document primarily addressed oncology studies; the reader is referred to the PLR Review Document produced by the Division of Biologic Oncology Products (DBOP) for a review of Oncology-related issues.

The algorithm used to analyze adverse events in the Chronic Renal Failure (CRF) patient population was derived directly from the FDA ADR Guidance. This algorithm was used to systematically analyze ADRs identified for Epoetin alfa (CRF ADR Justification Document submitted to BL 103234/0) and all adverse events from the combined active controlled studies with a subject incidence in the darbepoetin alfa group $\geq$ 2% greater than in the rHuEPO group. This analysis was performed for each adverse event by a group of 7 physicians (4 nephrologists and 3 internists) from 2 functional areas (Safety and Clinical Development) within Amgen.

The following parameters were included in the algorithm:

- frequency of reporting
- absolute and relative difference in subject incidence between the darbepoetin alfa and rHuEPO groups
- characteristics of the adverse event (eg, was the event typical of drug-induced adverse reactions)

- seriousness of the adverse event and propensity of the event to lead to clinical interventions, such as modification of the erythropoiesis-stimulating agent (ESA) dose
- plausibility of the event to be an ADR, based on the known pharmacology of the drug and available experimental data (ie, biological plausibility)
- subject incidence in randomized, placebo-controlled clinical trials in the other indication for darbepoetin alfa (ie, cancer patients on chemotherapy)
- known safety profile of other ESAs, based on the information contained in the European Summary of Product Characteristics for Eprex® (2006), NeoRecormon® (2007), Mircera® (2007), and Dynepo™ (2007)

Chronic Renal Failure Patients

The PLR uses an Adverse Reaction table as opposed to Adverse Event table. The FDA ADR Guidance outlines criteria for the classification of an Adverse Event as an Adverse Reaction. The submitted Adverse Reaction table was derived from analysis of adverse events from the following studies: 970200, 970235, 980202, 980117, and 980211. This data was submitted in tabular form in the document clinical-overview-adr.pdf.

Demographics

The median (range) age for subjects administered darbepoetin alfa was 62 (18 to 88) years. Fifty-five percent of subjects were male and 72% were white. Seventy-nine percent of subjects were receiving hemodialysis, 4% were receiving peritoneal dialysis, and 17% were not receiving dialysis.

A total of 1357 subjects (766 darbepoetin alfa, 591 rHuEPO) were included in the analyses. The mean duration of exposure for subjects receiving darbepoetin alfa was 302 days, with 580 subjects exposed for > 6 months and 360 subjects exposed for > 1 year. The median (25th, 75th percentiles) weight-adjusted dose of darbepoetin alfa was 0.50 (0.32, 0.81) μg/kg.

Methodology

In constructing the table, terms representative of the same phenomenon were grouped. Adverse events with greater incidence in the placebo group were not further analyzed. Adverse events with greater subject incidence in the Epogen group were further analyzed using an algorithm based on the FDA ADR Guidance Document. The following parameters were included in the algorithm.

- frequency of reporting
- absolute and relative difference in subject incidence between the Epoetin alfa and placebo groups
- characteristics of the adverse event (eg, was the event typical of drug-induced adverse reactions)
- severity/seriousness of the adverse event and propensity of the event to lead to clinical interventions, such as modification of the erythropoiesis-stimulating agent (ESA) dose

- plausibility of the event to be an ADR, based on the known pharmacology of the drug and available experimental data (ie, biological plausibility)
- subject incidence in randomized, placebo-controlled clinical trials in the other indications for Epoetin alfa (ie, cancer patients on chemotherapy, human immunodeficiency virus [HIV]-infected patients treated with zidovudine, surgery patients) (HIV/Oncology/Surgery ADR Justification Document)
- known safety profile of other ESAs, based on the information contained in the European Summary of Product Characteristics for Eprex® (2006), NeoRecormon® (2007), Mircera® (2007), and Dynepo™(2007)
- occurrence of the adverse event at a greater subject incidence in the high hemoglobin group in the Normal Hematocrit Cardiac Trial (NHCT; Amgen Study 930107) in dialysis subjects and the Correction of Hemoglobin and Outcomes in Renal Insufficiency study (CHOIR; J&JPRD Study PR00-06-014) in nondialysis subjects. Although these 2 outcome studies were not placebo-controlled and were performed after the initial Epoetin alfa BLA, data derived from these studies are relevant to the safety of CRF patients administered ESAs.

Adverse Reactions

The following adverse events were identified as ADRs for Epoetin alfa based upon analysis of adverse events reported in the randomized, double-blind, placebo-controlled studies included in the initial Epoetin alfa BLA alfa (CRF ADR Justification Document submitted to BL 103234/0).

- hypertension (ie, elevated blood pressure)
- thromboembolic events (ie, embolism and thrombosis)
- rash/erythema

The incidences of these events were similar or higher for darbepoetin alfa group compared with the rHuEPO group in the 5 combined active-controlled studies from the initial darbepoetin alfa BLA: 31% vs 26% for elevated blood pressure, 1% vs 1% for thrombosis and embolism, 5% vs 4% for rash/erythema. Therefore, these events are also considered ADRs for darbepoetin alfa.

Injection site pain was the only adverse event with a greater incidence in the darbepoetin alfa group that was considered an ADR specific for darbepoetin alfa. The incidence of injection site pain was 4% and 0% in the darbepoetin alfa and rHuEPO groups, respectively. This event was considered an ADR for darbepoetin alfa because it is biologically plausible that this is a darbepoetin alfa-specific reaction.

Events not considered by the sponsor to be adverse events were (incidence rates are for Aranesp vs Epogen, respectively, unless otherwise specified):

- Anemia
  - 7% vs 5%; but is related to drug efficacy rather than safety
- Infections

  - peritonitis (2% vs 0%); UTI (5% vs 3%); catheter site infection (4% vs 1%); bronchitis (7% vs 4%)
  - overall incidence of the infections and infestations organ system was 54% vs 53%
  - These infections were considered minor and not biologically plausible effects of ESAs

- Pruritis
  - 10% vs 6%; pruritis is not considered an ADR for other ESAs
- Renal Impairment
  - Renal Impairment (3% vs 0%), Renal Failure (2% vs 0%), and Azotemia (2% vs 1%) in the 5 combined studies
  - In non-dialysis study 980202 alone: 19% vs 0%, 9% vs 3%, 9% vs 5%, respectively
  - The following rationale was provided by the sponsor: "Renal impairment, renal failure, and azotemia had higher incidences in the darbepoetin alfa group compared with rHuEPO in the 5 combined studies (3% vs 0%, 2% vs 0%, and 2% vs 1%, respectively) (Appendix 2). The incidences for these events were 19% vs 0%, 9% vs 3%, and 9% vs 5%, respectively, in the nondialysis study (980202) alone. Although the results of CREATE (Drüeke et al, 2006) have prompted a debate regarding the effects of complete anemia correction on chronic kidney disease progression, it is well-recognized that partial correction of anemia with ESAs does not increase the rate of progression of chronic kidney diseases (Singh, 2007; Rossert and Froissart, 2006). More importantly, since these adverse events were observed in clinical studies using the same target hemoglobin concentrations for both treatment groups, considering these events ADRs for darbepoetin alfa would attribute the differences in incidences to the effects of a specific ESA, which is not clinically or biologically plausible. Animal data even suggest a protective role for darbepoetin on progression of nephropathies (Logar et al, 2007; Bahlmann et al, 2004). Importantly, administration of ESAs, including darbepoetin alfa, has not been linked with the occurrence of acute interstitial nephritis (Rossert and Fischer, 2006). Therefore, progression of renal disease is not considered an ADR for darbepoetin alfa."

The following events occurred at higher frequencies in the darbepoetin group vs Epogen.

- Vertigo (4% vs 1%)
- abdominal pain (9% vs 7%)
- fatigue (14% vs 10%)
- procedural hypotension (11% vs 8%)
- hemodialysis-induced symptoms (3% vs 1%)
- anorexia (5% vs 2%)
- dyspnea (17% vs 15%)
- hypotension (20% vs 17%)

However, for the following reasons, they were not considered ADRs:

- they lacked biological plausibility
- displayed minor absolute differences between groups, and
- displayed a general lack of severity (with the exception of dyspnea)

Heart Failure

The incidence of heart failure (cardiac failure) was 2% in the darbepoetin alfa group and 1% in the rHuEPO group. The difference between darbepoetin alfa and rHuEPO did not meet the criteria for further analysis as a possible ADR. However, the higher incidence of the high level 'heart failures' group term for darbepoetin alfa (5% vs 3%) in this analysis and the higher incidence of hospitalization due to congestive heart failure in the the high hemoglobin target group compared with the low hemoglobin target group in the CHOIR study are fully acknowledged. Furthermore, the description of the cardiovascular and thromboembolic events WARNINGS AND PRECAUTIONS section includes a discussion of heart failure. (b) (4)

Evaluation of Postmarketing Adverse Events

Aranesp® (darbepoetin alfa) has a postmarketing exposure of 2,045,000 patient-years over a period of approximately 6 years. Proposals for retention or revision of the current description of each event are summarized below.

Convulsion

The sponsor presents an analysis of the overal rate of convulsions in clinical trials of Epogen. It is noted that the reporting rate for convulsions is 2.66%-10% of patients with CKD and 2%-17% of patients on dialysis. In adult patients on dialysis, the risk of convulsions is highest within the first 90 days of Epogen therapy (2.5%). This may be related to the development of hypertensive encephalopathy due to a rapid increase in hemoglobin. Causes of convulsions in CKD patients may include uremia with malignant hypertension, pre-existing or acute focal cerebral lesion, fluctuations in the levels of anticonvulsant medications, metabolic encephalopathy related to uremia and dialysis, and acute aluminum toxicity.

In the course of Epogen studies involving 454 patients over 399 patient-years of therapy, 23 patients experienced 24 seizures or seizure-like activity. A total of 235 medically confirmed reports of convulsions were identified among patients receiving Epoetin alfa (154 from spontaneous sources, 81 from clinical or post-marketing studies). Assuming the accumulated number of Epogen users is 1,297,000 patients (3,435,000 patient-years)

since the drug launched in August 1989, then the crude reporting rate of convulsions for Epogen is ~4.48 per 100,000 patient-years.

In the course of Aranesp studies the subject incident rates were 1% in the treatment arms of patients with CKD, 0.6% in the treatment arms and 0.5% in the placebo arms of oncology patients. A total of 137 convulsion cases (107 from clinical trials, 8 from post-marketing studies, 22 from spontaneous reports) were identified among patients receiving Darbepoetin alfa or Aranesp. Assuming the accumulated number of Aranesp users were 1,774,000 (1,106,000 patient years) since the drug launched on 9/17/2001, then the crude reporting rates of convulsion for Aranesp was approximately 1.2×10^{-5} (2.0×10^{-5} per patient years) to 2.8×10^{-5} (2.5×10^{-5} per patient years) in CKD patients receiving Aranesp and 0.4×10^{-5} (1.1×10^{-5} per patient years) in oncology patients.

Because re-challenge (with either Epogen or Aranesp) was associated with recurrent seizure and despite that fact that many patients had either pre-existing risk factors for-, or pre-existing-, seizure disorder the sponsor acknowledges the possibility of a causal relationship between ESA treatment and seizure.

In terms of convulsion (seizure), because the rates between control and ESA arms were similar (< 1% difference), convulsion/seizure was not included in the proposed ADR table. However, seizure is listed in other areas of the label (Sections 5.4 and 6.0).

Allergic Reaction

Epoetin alfa

The search of ARISg Safety Database identified 186 medically confirmed reports containing 207 events. Reports of event urticaria without any other symptoms associated with angioedema were excluded. The final dataset consisted of 84 reports containing 101 events, 27 of which were serious reports and 74 were non-serious reports.

Analysis of Epoetin-related Study Reports

Three reports were identified from Epoetin alfa studies. The events included angioneurotic oedema, face oedema, and tongue oedema. None of the events were reported with a causal relationship to Epoetin alfa therapy nor did those cases have rechallenge/dechallenge information. The angioneurotic oedema (COV064213) was a suspected allergic reaction to Taxol and/or Carboplatin taken for stage IIIc ovarian cancer with malignant ascites related to metastatic adenocarcinoma. The face oedema (US155814) was due to a deep vein thrombosis in a recently placed internal jugular dialysis catheter. The tongue oedema (210960) was due to a biopsy of a non-healing left lateral tongue ulcer in a subject with AIDS, multiple opportunistic infections, and a recent history of bacterial sinusitis; the subject died due to complications associated with thrombocytopenia secondary to the tongue biopsy.

Using the number of reports (n=3) from study sources as the numerator and the subjectexposure rate of 4,381 subject-years through 31 December 2006 as the

denominator, the incidence rate of angioedema in subjects exposed to Epoetin alfa was 0.68 per 1,000 subject years.

Analysis of Epoetin-related Non-Study Reports

There were 81 reports related to Epogen with 98 events identified from non-study sources. Of the 98 events, 24 were serious events and 74 were non-serious events.

Using the number of reports from non-study sources (n=81) as the numerator and the subject exposure rate of 3,707,000 patient-years through 31 December 2006 as the denominator, the reporting rate of angioedema in subjects on Epoetin alfa therapy was 2.18 per 100,000 patient years.

Darbepoetin alfa

The search of ARISg Safety Database identified 117 reports containing 137 events which met the criteria detailed above. Of the 137 events, 122 were medically confirmed and 15 were not medically confirmed. The 15 medically unconfirmed events were excluded from the final dataset. In addition, reports of event urticaria without any other symptoms associated with angioedema were also excluded. The final exclusion resulted in a data set consisted of 58 reports, 33 serious and 25 non-serious cases.

Analysis of Aranesp-related Study Reports

A total of 15 serious reports were identified from study sources. Reporter causality assessment was reported as not related or unlikely related in all 15 reports. Other causative factors included concomitant chemotherapeutic agents (e.g., Taxol, carboplatin) and medications (e.g., tixocortol, bacitracin, aspirin, carticaine, pentoxifylline, flucloxicilin, and codeine), food allergy, history of Quincke's oedema, blood transfusion, and exposure to contrast media.

Using the number of reports from study sources (n=15) as the numerator and the subject exposure rate of 11,768 subject-years through 31 December 2006 as the denominator, the incidence rate of angioedema in subjects exposed to darbepoetin alfa therapy was 1.27 per 1,000 subject-years (0.127%).

Analysis of Aranesp-related Non-Study Reports

There were 43 reports related to Darbepoetin alfa from non-study sources, 18 serious and 25 nonserious reports. Of the 43 reports, 7 had positive rechallenge.

Using the number of reports (n=43) for Aranesp® from non-study as the numerator and the patient exposure rate (2,607,000 patients or 1,644,000 patient-years) through 31 December 2006, the reporting rate of event angioedema in patients with anemia on darbepoetin alfa therapy is 2.61 per 100,000 patient-years.

Sponsor Conclusion Regarding Allergic Reaction Labeling

Allergic reaction is included as a potential ADR in the current darbepoetin alfa USPI. Recent analyses suggest that angioedema and anaphylactic reaction are, in rare cases, ADRs for darbepoetin alfa. Although very few cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported for patients receiving ESAs, a recent analysis of postmarketing cases indicates that a causal relationship cannot be reasonably established between treatment with darbepoetin alfa and either of these events. Therefore, Amgen suggests retaining allergic reaction as an ADR identified through postmarketing reports, but revising the relevant statement in the WARNINGS AND PRECAUTIONS section to specify that reports of serious allergic reactions, including angioedema and anaphylactic reaction, have been associated with darbepoetin alfa. Proposed language is provided in the draft USPI.

Pure Red Cell Aplasia

As reflected in the current darbepoetin alfa USPI, treatment with ESAs may, in very rare cases, induce the production of neutralizing anti-ESA antibodies responsible for pure red cell aplasia (Bennett et al, 2004, Casadevall et al, 2002). Therefore, Amgen proposes that the current statements in the WARNINGS AND PRECAUTIONS section, which accurately reflect this ADR, be retained.

Medical Officer Review of All Adverse Events Reported in Studies 970200, 970235, 980117, 980211, and 980202 (Subjects with CRF Either Not Receiving Dialysis or Receiving Dialysis)

The following tables (1-6) represent Medical Officer review of the sponsor's submitted adverse event synopsis from the above stated studies. System Organ Class (SOC), High Level Group Term (HLGT), and Preferred Terms (PT) $\geq$ 5% were included. Additionally, PTs of interest (such as those pertaining to hypertension, convulsion, or thrombosis) were also noted. Tables 2-5 are followed by brief discussion related to the individual member terms.

Some SOCs were of $\geq$ 5% but were not further substantiated by biologic plausibility related to the mechanism of action of ESAs. It is additionally noted that many of these events share very similar rates between treatment groups. The following SOC groups of $\geq$ 5% in either rHuEPO or Darbepoetin alfa were therefore excluded from further analysis:

Table 1: SOCs with 5% or Greater Incidence in Either Epogen or Darbepoetin Excluded from Further Analysis

SYSTEM ORGAN CLASS High Level Group Term *Preferred Term*	rHuEPO **(N = 591)**	darbepoetin alfa **(N = 766)**
EAR AND LABYRINTH DISORDERS	**27 (5)**	**53 (7)**
EYE DISORDERS	**49 (8)**	**99 (13)**
Ocular Infections, Irritations And Inflammations	19 (3)	39 (5)
INFECTIONS AND INFESTATIONS	**313 (53)**	**411 (54)**
Bacterial Infectious Disorders	40 (7)	54 (7)
Infections - Pathogen Class Unspecified	274 (46)	355 (46)
Nasopharyngitis	85 (14)	94 (12)
Upper Respiratory Tract Infection	56 (9)	54 (7)
Bronchitis	26 (4)	50 (7)
Urinary Tract Infection	20 (3)	40 (5)
Viral Infectious Disorders	63 (11)	77 (10)
Influenza	38 (6)	45 (6)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**299 (51)**	**375 (49)**
Joint Disorders	67 (11)	88 (11)
Arthralgia	54 (9)	62 (8)
Muscle Disorders	174 (29)	222 (29)
Muscle Spasms	149 (25)	202 (26)
Musculoskeletal And Connective Tissue Disorders NEC	158 (27)	202 (26)
Pain In Extremity	81 (14)	99 (13)
Back Pain	57 (10)	64 (8)
Shoulder Pain	24 (4)	41 (5)
PSYCHIATRIC DISORDERS	**81 (14)**	**105 (14)**
Anxiety Disorders And Symptoms	27 (5)	26 (3)
Sleep Disorders And Disturbances	32 (5)	46 (6)
Insomnia	31 (5)	40 (5)

The following SOCs (Tables 2-5) displayed rates ≥ 5% in either Epogen or Darbepoetin treated groups, or contained Preferred Terms of special interest.

Table 2: SOCs Occurring at ≥ 5% or Containing Terms of Special Interest

SYSTEM ORGAN CLASS High Level Group Term *Preferred Term*	rHuEPO **(N = 591)** n (%)	darbepoetin alfa **(N = 766)** n (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**38 (6)**	**61 (8)**
Anaemias Nonhaemolytic And Marrow Depression	33 (6)	51 (7)
Anaemia	31 (5)	51 (7)
CARDIAC DISORDERS	**150 (25)**	**194 (25)**
Cardiac Arrhythmias	82 (14)	97 (13)
Coronary Artery Disorders	62 (10)	84 (11)
Angina Pectoris	44 (7)	64 (8)
Myocardial Infarction	8 (1)	15 (2)
Angina Unstable	5 (1)	8 (1)
Coronary Artery Disease	5 (1)	6 (1)
Acute Myocardial Infarction	4 (1)	2 (0)
Heart Failures	16 (3)	38 (5)
GASTROINTESTINAL DISORDERS	**325 (55)**	**444 (58)**
Gastrointestinal Motility And Defecation Conditions	156 (26)	205 (27)
Diarrhoea	125 (21)	163 (21)
Constipation	47 (8)	56 (7)
Gastrointestinal Signs And Symptoms	247 (42)	314 (41)
Nausea	114 (19)	139 (18)
Vomiting	120 (20)	136 (18)
Abdominal Pain	42 (7)	71 (9)
Abdominal Pain Upper	47 (8)	46 (6)

Because Anemia relates more to treatment *effect* it is reasonable to exclude it from further analysis. Biologic plausibility is absent for cardiac arrhythmia, but preferred terms related to coronary artery thrombosis are plausible. The overall rate for Coronary Artery Disorders, however, is basically equal between groups; cardiovascular events are a major part of the Black Box Warning section of the label. **It is recommended that Angina Pectoris (8%) appear in the Adverse Reaction Table.**

In terms of Gastrointestinal Disorders – their presence is not substantiated by biological plausibility, but many of these items are listed in the currently approved product label. It is noted that the incidence of events between groups, while higher than 5% even at the preferred term level, is basically equal.

Table 3: SOCs Occurring at ≥ 5% or Containing Terms of Special Interest

SYSTEM ORGAN CLASS High Level Group Term *Preferred Term*	rHuEPO **(N = 591)** n (%)	darbepoetin alfa **(N = 766)** n (%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**323 (55)**	**443 (58)**
Administration Site Reactions	62 (10)	106 (14)
Body Temperature Conditions	73 (12)	93 (12)
Pyrexia	54 (9)	71 (9)
General System Disorders NEC	274 (46)	362 (47)
Oedema Peripheral	93 (16)	127 (17)
Fatigue	62 (10)	105 (14)
Asthenia	51 (9)	66 (9)
Malaise	35 (6)	43 (6)
Face Oedema	27 (5)	22 (3)
Pain	33 (6)	22 (3)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**284 (48)**	**364 (48)**
Bone And Joint Injuries	29 (5)	40 (5)
Injuries NEC	80 (14)	101 (13)
Fall	27 (5)	35 (5)
Procedural And Device Related Injuries and Complications NEC	228 (39)	292 (38)
Procedural Hypotension	49 (8)	(b) (4)
Vascular Access Complication	63 (11)	63 (8)
Arteriovenous Graft Thrombosis	52 (9)	40 (5)
Arteriovenous Fistula Site	24 (4)	38 (5)
Vascular Graft Complication	37 (6)	16 (2)
INVESTIGATIONS	**80 (14)**	**93 (12)**
Cardiac And Vascular Investigations (Excluding Enzyme Tests)	45 (8)	49 (6)
Physical Examination Topics	27 (5)	26 (3)

Pyrexia, Fatigue, Asthenia, and Malaise are common in the studied population. Pain is a nonspecific term. These events occur at equal to- or lesser- rates in the darbepoetin treated group compared to the Epogen group. Administration site reactions and terms related to edema maintain biologic plausibility. **It is recommended that Peripheral Edema (17%) appear in the Adverse Reactions table.**

While Bone and Joint Injuries are not plausible reactions of ESA therapy, Procedural and Device Related Injuries and Complications are. **It is recommended that Procedural Hypotension (b) (4) and Vascular Access Complication (8%) appear in the Adverse Reactions table.**

Investigations, while ≥ 5%, occur at equal or lesser rates among Darbepoetin treated subjects.

Table 4: SOCs Occurring at ≥ 5% or Containing Terms of Special Interest

SYSTEM ORGAN CLASS High Level Group Term *Preferred Term*	rHuEPO **(N = 591)** n (%)	darbepoetin alfa **(N = 766)** n (%)
METABOLISM AND NUTRITION DISORDERS	**120 (20)**	**185 (24)**
Appetite And General Nutritional disorders	37 (6)	70 (9)
Anorexia	14 (2)	36 (5)
Electrolyte And Fluid Balance Conditions	63 (11)	94 (12)
Fluid Overload	48 (8)	51 (7)
NERVOUS SYSTEM DISORDERS	**233 (39)**	**327 (43)**
Headaches	109 (18)	155 (20)
Headache	107 (18)	149 (19)
Central Nervous System Vascular Disorders	15 (3)	27 (4)
Cerebrovascular Accident	6 (1)	9 (1)
Transient Ischaemic Attack	2 (0)	5 (1)
Cerebral Infarction	2 (0)	3 (0)
Brain Stem Infarction	1 (0)	1 (0)
Cerebellar Infarction	0 (0)	1 (0)
Cerebral Ischaemia	1 (0)	1 (0)
Neurological Disorders NEC	139 (24)	178 (23)
Dizziness	85 (14)	96 (13)
Seizures (Incl Subtypes)	10 (2)	12 (2)
RENAL AND URINARY DISORDERS	**38 (6)**	**94 (12)**
Renal Disorders (Excl Nephropathies)	7 (1)	54 (7)
Renal Impairment	0 (0)	25 (3)
Renal Failure	1 (0)	13 (2)
Azotaemia	4 (1)	12 (2)
Renal Failure Chronic	0 (0)	4 (1)
Urinary Tract Signs And Symptoms	29 (5)	40 (5)

Metabolism and Nutritional Disorders was included for due to the presence of the HLGT Electrolyte and Fluid Balance Conditions. Fluid overload bears biologic plausibility to the increased hematocrit/viscosity, and possible vascular endothelial effects of ESA therapy. **It is recommended that Fluid Overload (7%) appear in the Adverse Reaction table.**

The Nervous System SOC was included due to its preferred terms of interest – namely those occurring under the HLGT Central Nervous System Vascular Disorders. While less than 5% in both groups, this HLGT is addressed by the Black Box Warning section of the label.

Renal and Urinary Disorders SOC is addressed in the sponsor's rationale for exclusion of these events (see Renal Impairment section of the Adverse Reactions portion of this document). The sponsor's rationale appears acceptable. Additionally, none of the PT members of this HLGT exceeded 5%.

Table 5: SOCs Occurring at ≥ 5% or Containing Terms of Special Interest

SYSTEM ORGAN CLASS High Level Group Term *Preferred Term*	rHuEPO **(N = 591)** n (%)	darbepoetin alfa **(N = 766)** n (%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**229 (39)**	**291 (38)**
Lower Respiratory Tract Disorders (Excl Obstruction & Infection)	23 (4)	42 (5)
Pulmonary Oedema	14 (2)	25 (3)
Pulmonary Congestion	7 (1)	8 (1)
Respiratory Disorders NEC	189 (32)	246 (32)
Dyspnoea	90 (15)	130 (17)
Cough	70 (12)	95 (12)
Upper Respiratory Tract Disorders (Excluding Infections)	45 (8)	42 (5)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**152 (26)**	**211 (28)**
Epidermal And Dermal Conditions	102 (17)	151 (20)
Pruritus	35 (6)	75 (10)
Rash	13 (2)	28 (4)
VASCULAR DISORDERS	**265 (45)**	**376 (49)**
Decreased And Nonspecific Blood Pressure Disorders and Shock	104 (18)	163 (21)
Hypotension	103 (17)	156 (20)
Vascular Hypertensive Disorders	143 (24)	228 (30)
Hypertension	142 (24)	224 (29)
Embolism And Thrombosis	5 (1)	5 (1)
Thrombophlebitis	0 (0)	2 (0)
Embolism	0 (0)	1 (0)
Thrombosis	0 (0)	1 (0)
Venous Thrombosis Limb	1 (0)	1 (0)
Deep Vein Thrombosis	2 (0)	0 (0)
Thrombophlebitis Superficial	1 (0)	0 (0)
Vena Cava Thrombosis	1 (0)	0 (0)

Respiratory, Thoracic, and Mediastinal Disorders SOC is included for the potential for ESA therapy to increase blood pressure and viscosity thus inducing ventricular strain. **It is recommended that Dyspnea (17%) and Cough (12%) appear in the Adverse Reaction table.**

Skin and Subcutaneous Tissue Disorders SOC is further addressed by the sponsor with the inclusion of Rash/Erythema. This issue is addressed by the sponsor in Table 6.

Vascular Disorders SOC – particularly Hypertension and Embolism and Thrombosis, are further addressed below in Table 6, which was produced by the sponsor following more

extensive review of related terms. The Sponsor adequately addresses these rates in the proposed Adverse Reaction table.

The sponsor sets forth the following table highlighting rates for events of particular interest.

Table 6: Special Interest AEs by Treatment Group for Studies in Patients with CRF

Special Interest AEs by Treatment Group for Studies 970200, 970235, 980117, 980211, and 980202		
ALL ADVERSE EVENTS OF SPECIAL INTEREST	rHuEPO (N = 591) n (%)	darbepoetin alfa (N = 766) n (%)
Number of Subjects Reporting Adverse	228 (39)	325 (42)
Events		
ELEVATED BLOOD PRESSURE	152 (26)	236 (31)
EMBOLISM AND THROMBOSIS	6 (1)	9 (1)
RASH	21 (4)	36 (5)
RASH AND ERYTHEMA	24 (4)	42 (5)
VASCULAR ACCESS THROMBOSIS	81 (14)	77 (10)

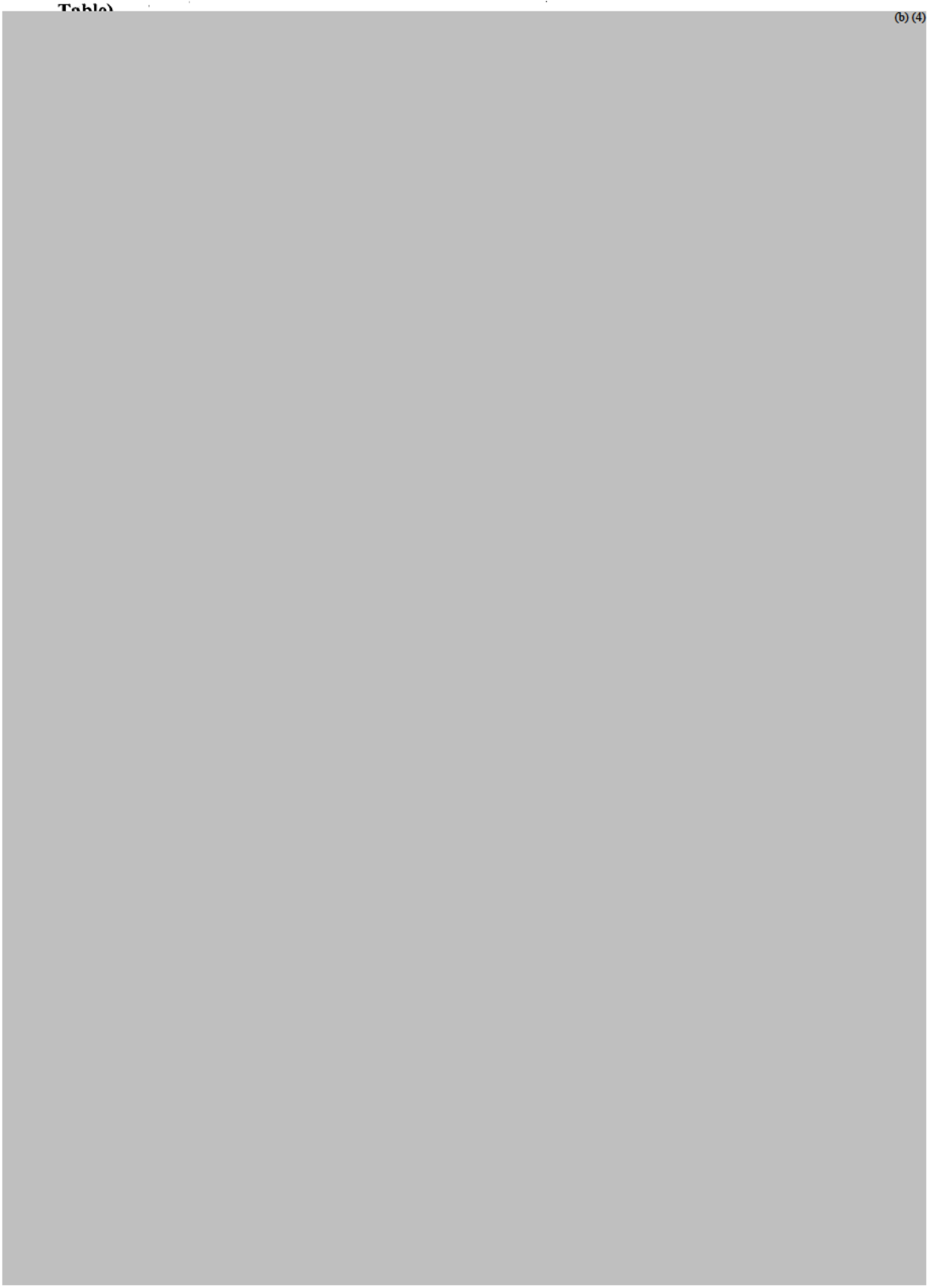
n,%: number and percentage of subjects reporting any adverse event in the special interest category
Note: Percentages based on N
Elevated Blood Pressure = vascular hypertensive disorders, blood pressure increased, blood pressure diastolic increased, blood pressure systolic increased
Vascular Access Thrombosis = arteriovenous graft thrombosis, arteriovenous fistula thrombosis, graft thrombosis, shunt thrombosis, arteriovenous fistula occlusion, vascular graft occlusion
Rash = rash, rash pruritic, rash macular, rash generalized, rash erythematous, rash papular
Rash and Erythema = rash, rash pruritic, rash macular, rash generalized, rash erythematous, rash papular, erythema
Embolism and Thrombosis = embolism and thrombosis, venous occlusion, superior vena caval occlusion, phlebitis, periphlebitis, phlebitis superficial
Program: /userdata/stat/nesp/meta/FDA/PI_Dec2007/analysis/tables/t_sa_ae_spec_int.sas
Output: t_sa_ae_spec_int.rtf (Date Generated: 10DEC07:13:00:21) Source Data: /userdata/stat/nesp/meta/FDA/PI_Dec2007/analysis/statdata/sdf

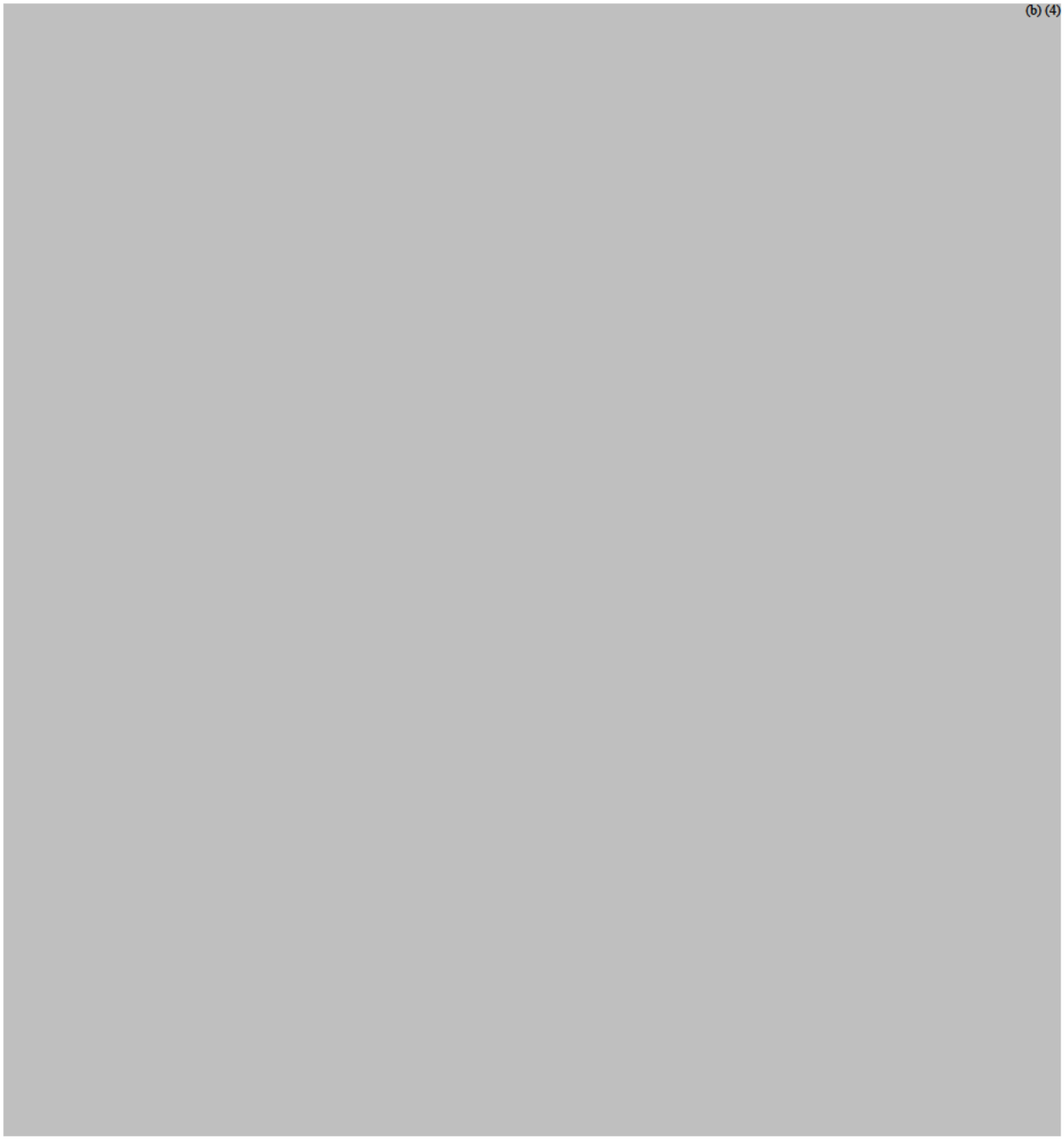
Proposed Adverse Reactions Table

Table 7 depicts the proposed modifications superimposed on the currently approved Adverse Event table for CRF patients.

Table 7: Sponsor Proposed Adverse Reactions Table (Superimposed on Current Adverse Events Table)

(b) (4)





Conclusion

Following review of the submitted materials, it is recommended that the following Adverse Reactions be added to the Sponsor's proposed Adverse Reaction table:

- **Angina Pectoris (8%)**
- **Peripheral Edema (17%)**
- **Procedural Hypotension** (b) (4)
- **Vascular Access Complication (8%)**
- **Fluid Overload (7%)**
- **Dyspnea (17%)**
- **Cough (12%)**

3. Labeling Review: Submitted PLR for Darbepoetin alfa (Aranesp)

The submitted PLR was reviewed by DMIHP and jointly with Division of Biologic Oncology Products (DBOP) in a series of labeling meetings culminating in the most current DMIHP/DBOP version. This review document focuses on changes made specifically to DMIHP pertinent sections; reference is made to the PLR Labeling Comments document prepared by DBOP.

In reviewing the submitted PLR document, the following resources were used:

- §CFR 201.57,
- "Overview of New Labeling Requirements", available at: http://cdernet.cder.fda.gov/OND/SEALD/PM_PLR_training_2006/Irisslides.htm
- Label Review Tool (LRT), available at: http://cdernet.cder.fda.gov/OND/SEALD/PM_PLR_training_2006/Jeanne's%20slides-%20LRTPresentation.10.19.06.htm
- Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format http://www.fda.gov/cder/guidance/5537fnl.pdf

Basic tenets guiding the DMIHP revision were:

- The use of active voice
  - As much as possible, phrases and sentences in the submitted PLR which were in passive voice were converted to active voice
- Concise presentation
  - The Division attempted to rephrase and restructure elements of the revised PLR to be more relevant to the sections and subsections in which they appeared.
  - The Division attempted to reduce language pertaining to 'practice of medicine' issues
- Emphasis on readability and clarity
  - Material not directly related to subsections was moved to more appropriate subsections
  - Sections presenting complex material (such as dose adjustment) were simplified and bulleted
  - Increased 'white space' was emphasized to improve readability
- Emphasis on preferred terminology and Phrases
  - Throughout the document, the term *Adverse Reaction(s)* was preferred over *Adverse Event(s)* in keeping with current PLR guidelines
  - The Division did not list *Theoretical Risks* except where required

Highlights Section

Recent Major Changes

Reviewer's Comment(s):

- Following discussion between DMIHP and DBOP, this section was omitted because it contained no *major* changes, nor did such a section appear to pertain to the *first* PLR for this drug.

Indications and Usage
Reviewer's Comment(s):

- In this section and throughout the document, the phrase [redacted] (b) (4) was changed to [redacted] (b) (4) to improve clarity regarding the source of anemia for which Aranesp is indicated.

Dosage and Administration
Reviewer's Comment(s):

- Basic reformatting for clarity, but otherwise no major changes.

Contraindications
Reviewer's Comment(s):

- [redacted] (b) (4)" was removed. PLR Labeling Review Tool (LRT) advises avoidance of the inclusion of theoretical contraindications.
- This section was expanded to include contraindications of clinical importance (Uncontrolled Hypertension, PRCA, Serious Allergic Reactions to Aranesp).

Warnings and Precautions
Reviewer's Comment(s):

- The PLR LRT advises that this section contain "information that would affect decisions about whether to prescribe the drug, recommendations for patient monitoring that are critical to safe use of the drug, and measures that can be taken to mitigate harm".
- Information was therefore included regarding hyporesponsiveness, hypertension management, level of hemoglobin at initiation of therapy in cancer patients, and dialysis management.

Adverse Reactions
Reviewer's Comment(s):

- Adverse reactions occurring in ≥ 10% of Aranesp-treated patients in clinical studies were noted.

Use in Specific Populations
Reviewer's Comment(s):

- This section was added to the Highlights portion of the PLR and addresses use of Aranesp in Pregnancy, Nursing Mothers, and Pedriatric use.

Full Prescribing Information

Indications and Usage (1):
Reviewer's Comment(s):

- Subsections were shortened and dose initiation and adjustment information was bulleted for improved readability.

Dosage and Administration (2)

Reviewer's Comment(s):

- *2.1 General* was added and contains iron monitoring/supplementation information deemed applicable to all indications for Epogen. Iron monitoring/ supplementation information was then removed from other sections (ie, *Surgery Patients*).
- The basic *intent* of the sponsor submitted PLR label was maintained throughout the Dosage and Administration section, but an emphasis was placed on concise presentation of material with increased white space and bulleting when appropriate.
- Cancer Patients Receiving Chemotherapy was also reviewed jointly with DBOP – reference is made to the DBOP Aranesp PLR Review Document.

- In *Preparation and Administration* section was converted to a bulleted format for improved readability – no major changes were made.

Dosage Forms and Strengths (3)

Reviewer's Comment(s):

- No major changes.

Contraindications (4)

Reviewer's Comment(s):

- This section was expanded to more clearly state populations in whom Epogen should not be used. See Above description under Highlights.

Warnings and Precautions (5)

Reviewer's Comment(s):

- No major changes were made to sections of 5.1 relevant to DMIHP.
- See the DBOP PLR Labeling Comments for their revisions to 5.2.
- The *Warnings and Precautions* subsections subsequent to 5.2 were reordered from most to least severe: *Hypertension (5.3), Seizures (5.4), Pure Red Cell Aplasia (5.5), Serious Allergic Reactions* ((b) (4)
- Dose adjustment material was deleted from section 5.3 due to redundance (already in Dosage and Administration). Amgen is asked to provide data on hypertensive encephalopathy for this section, if it exists.
- *5.8 Hematology* section was replaced with 5.9 *Laboratory Monitoring.* Information contained within *Hematology* is already contained elsewhere (*Pharmacodynamics* and *Laboratory Monitoring*).
- *5.12 Laboratory Tests* was consolidated into *Laboratory Monitoring.*

Adverse Reactions (6)

Reviewer's Comment(s):

- *Serious Allergic Reactions* was added to the Adverse Reactions bulleted list; the list was reordered in terms of severity

Clinical Study Reports (6.1)
Reviewer's Comment(s):

- The Adverse Reactions Section was modified as recommended in the above discussion.

Postmarketing Experience (6.2)
Reviewer's Comment(s):

- No major changes made.

Immunogenicity (6.3)
Reviewer's Comment(s):

- Amgen, please insert data regarding incidence/prevalence of immunogenicity, if available.

Drug Interactions (7)
Reviewer's Comment(s):

- No changes made.

Use in Specific Populations (8)
Pregnancy (8.1) and Nursing Mothers (8.3)
Reviewer's Comment(s):

- Modified according to Maternal Health Team comments.

Pediatric Use (8.4) and Geriatric Use (8.5)
Reviewer's Comment(s):

- See DBOP PLR Review Document for changes made to Pediatric Cancer Patients on Chemotherapy.
- No major changes made to Pediatric CRF Patients or Geriatric Patients.

Overdosage (10)
Reviewer's Comment(s):

- This section was shortened; contents related to reinitiation of dosing, dose adjustment, and rate-of-rise of hemoglobin were deemed more appropriate for *Dosage and Administration*

Description (11) and Pharmacology (12)
Reviewer's Comment(s):

- Aspects of these sections (which are somewhat related) were combined under *Description*. The basic message was left intact.

Nonclinical Toxicology (13)
Carcinogenesis, Mutagenesis, Impairment of Fertility (13.1)

Reviewer's Comment(s):

- No Major Changes

Reproductive and Developmental Toxicology (13.3)

Reviwer's Comment(s):

- This section was created with input from MHT and information from the sponsor's submitted section 8.1.

Clinical Studies (14)

Chronic Renal Failure Patients (14.1)

Reviewer's Comment(s):

- No major changes.
- See DBOP Review Document regarding 14.2 (Cancer patients receiving chemotherapy).

(b) (4) Surgery Patients (14.4)

Reviewer's Comment(s):

- (b) (4)
- No major changes were made to the Surgery Patients Section.

Cancer Patients on Chemotherapy (14.3)

Reviewer Comment(s):

- See DBOP PLR Review Document.

How Supplied/Storage and Handling (16), Patient Counseling Information (17)

Reviewer's Comment(s):

- No major changes to 16
- 17 is modified for consistency with the Epogen label.

4. Conclusions

Overall, the submitted revisions appear acceptable. In review of the submitted data, it was determined that the Adverse Reactions table submitted by the sponsor did not accurately represent the data. Modifications to the Adverse Reaction table were counter-proposed and appear above. The sponsor is asked to revise the table accordingly.

5. Recommended Regulatory Action

It is recommended that the above stated modifications be made to the Adverse Reactions Table pertaining to CRF patients.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 3, 2008

From: Monica Hughes, M.S., DBOP/OODP/CDER

Subject: Initial RPM PLR Review: sBLA 103951/5173 (Aranesp PI)

Upon review of the Aranesp package insert labeling submitted in PLR format by Amgen, Inc. on December 26, 2007, in the sBLA filing, I have the following comments with respect to the format of the PLR label. None of my comments pertain to content or review related issues.

Please note, all content related discussions will occur during team labeling meetings.

With Respect to the Highlights of Prescribing Information Section of the Package Insert:

1. "Aranesp (darbepoetin alfa)" appears under the highlights limitation statement, however, (b) (4) route of administration is NOT listed in the line below as required for biological products (21 CFR 600.3 (k)). Please revise.

2. The black box warning reads (b) (4) Please revise.

3. Under the INDICATIONS AND USAGE section, please define "ESA", Erythropoiesis stimulating agents, as the pharmacologic class.

4. Under Warnings and Precautions, Amgen listed: Hypertension, PRCA, Allergic reactions, and Seizures. Is it acceptable to not list "Increased Mortality, Serious Cardiovascular and Thromboembolic Events" and "Increased Mortality and/or Tumor Progression."

5. Comment: the "Revised:_____" will need to be revised to reflect the date in which this supplement is ultimately approved.

6. Please note, the revision date at the end of the highlights section replaces the "revision" or "issued" date at the end of the labeling. It should not appear in both places, please delete the "Revision Date: *month* 2007" from the end of the label.

With Respect to the FULL PRESCRIBING INFORMATION:

7. Please review the Full Prescribing sections of the label for consistency with respect to reference citations. Please ensure all citations follow the following format: [*see Section referring to* (section number, e.g. 5.2)].

With Respect to the FULL PRESCRIBING INFORMATION: CONTENTS* and FULL PRESCRIBING INFORMATION Sections of the Package Insert:

BOXED WARNING: In both the TOC and the boxed Warning in the FPI

8. The black box warning reads [redacted (b) (4)] Please revise.

DOSAGE AND ADMINISTRATION:

8. We recommend avoiding use of Latin abbreviations such as IV, while you do define IV in the first sentence of this section; you subsequently use the abbreviation throughout the label. We recommend always using [redacted (b) (4)] to avoid a greater potential for medication errors should the abbreviation be misread.

9. Immediately following the heading, Amgen has inserted the following text: [redacted (b) (4)] Should this sentence be deleted?

10. With respect to the specific content for parenteral products as outlined on page 15 of the LRT, under section 2.3 "**Preparation and Administration**" the first paragraph is incorrect and should be revised accordingly: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration [redacted (b) (4)]

CONTRAINDICATIONS:

11. Each contraindication should have its own subheading. In addition, each contraindication, if not just a theoretical possibility, should also contain the type and nature of the expected adverse reaction along with information regarding its known prevalence rate.

WARNINGS AND PRECAUTIONS:

12. [redacted (b) (4)]

ADVERSE REACTIONS:

13. We note that all adverse events tables have been deleted from your proposed draft labeling. We recommend that you retain adverse event tables that depict the most common adverse event rates to that of placebo. This is ultimately a review issue and will be discussed further during labeling negotations.

14. With respect to subsection "**6.3, Immunogenicity**", this section should be revised to include the verbatim statement: "As with all therapeutic proteins, there is potential for immunogenicity. [Insert data from PI.] The incidence of antibody formation is highly dependent on the sensitivity and the specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Aranesp with the incidence of antibodies to other products may be misleading."

OTHER COMMENTS:

15. Please note that the revision date at the end of the highlights section replaces the "revision" or "issued" date at the end of the PI or attached PPI. Please delete the "Issued Date" from the end of the PPI.

BLA/BLS Regulatory Filing Review

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CDER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy . An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD)..

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications.

CDER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: 103951/5173 (b) (4) Product: darbepoetin alfa Applicant: Amgen

Final Review Designation (circle one): (Standard) Priority

Submission Format (circle all that apply): Paper (Electronic) Combination

Submission organization (circle one): Traditional (CTD)

Filing Meeting: Date 2/11/08 Committee Recommendation (circle one): (File) RTF

For BLA and Efficacy BLS: Were any potential review issues identified? (Yes) No

RPM: _____ 2/11/08
(signature/date)

Attachments:

- ☑ Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):
  - X Part A – RPM
  - ____ Part B – Product/CMC/Facility Reviewer(s): _____ _____ _____
  - X Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): Zhou _____
  - X Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical) Reviewers Schaefer Lee _____ _____
- ☐ Memorandum of filing recommendation:
  - ____ Part B – Product/CMC/Facility Reviewer(s): _____ _____ _____
- ☑ Memo of Filing Meeting

STN 103851/5773 (b) (4) Product darbepoetin alfa Part A Page 1

Applicant:	Amgen
Short Summary:	to reinstate PE + PPI based on recommendation at 5/10/07 DAC mtg
RPM:	
Office/Division:	OODP/DBOP

Filing worksheet Part A. Regulatory Project Manager (RPM)

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y N	
Form 356h completed ❑ including list of all establishment sites and their registration numbers ❑ If foreign applicant, US Agent signature.	Y N Y N Y N	was submitted upon request
Comprehensive Table of Contents	Y N	
Debarment Certification with correct wording (see * below)	Y N	
User Fee Cover Sheet	Y N	(b) (4) -unbundled from 5773
User Fee payment received	Y N	
Financial certification &/or disclosure information	Y N	
Environment assessment or request for categorical exclusion (21 CFR Part 25)	Y N	Not included - need to request
Pediatric rule: study, waiver, or deferral	Y N	N/A
Labeling: ❑ PI –non-annotated ❑ PI –annotated ❑ PI (electronic) ❑ Medication Guide ❑ Patient Insert ❑ package and container ❑ diluent ❑ other components ❑ established name (e.g. USAN) ❑ proprietary name (for review)	Y N Y N Y N Y N Y N Y N Y N Y N Y N Y N Y N	

* The Debarment Certification must have correct wording , e.g. "I, the undersigned, hereby certify that XXX Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug, and Cosmetic Act in connection with the studies listed in Appendix XXX." Applicant may not use wording such as "To the best of my knowledge,.."

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y N	

STN 103451/5173 (b) (4) Product darbepoetin alfa Part A Page 2

Examples of Filing Issues	Yes?	If not, justification, action & status
❑ legible	Y N	
❑ English (or translated into English)	Y N	
❑ compatible file formats	Y N	
❑ navigable hyper-links	Y N	
❑ interpretable data tabulations (line listings) & graphical displays	Y N	
❑ summary reports reference the location of individual data and records	Y N	
❑ protocols for clinical trials present	Y N	
❑ all electronic submission components usable (e.g. conforms to published guidance)	Y N	
companion application received if a shared or divided manufacturing arrangement	Y N	
if CMC supplement:		
❑ description and results of studies performed to evaluate the change	Y N	
❑ relevant validation protocols	Y N	
❑ list of relevant SOPs	Y N	
if clinical supplement:		
❑ changes in labeling clearly highlighted	Y N	
❑ data to support all label changes	Y N	
❑ all required electronic components, including electronic datasets (e.g. SAS)	Y N	
if electronic submission:		
❑ required paper documents (e.g. forms and certifications) submitted	Y N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Has orphan drug exclusivity been granted to another drug for the same indication?
If yes, review committee informed? No

Does this submission relate to an outstanding PMC? ND

STN 103451/5173 (b) (4) Product darbepoetin alfa Part A Page 3

If an Advisory Committee (AC) discussion may be needed, list applicable AC meetings scheduled to occur during the review period:

- Name: N/A
- Dates: _____

Recommendation (circle one): File RTF

RPM Signature: _____ 2/1/08

Chief, Project Management Staff concurrence: _____