CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103234Orig1s5166

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 Acting Team Leader, Patient Labeling Reviewer **Division of Risk Management** Barbara Fuller 4/2011
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Risk Management** Sharon R. Mills 4/20/11
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.

Page(s) of Draft Labeling has been Withheld in Full immediately following this page as B4 (CCI/TS)

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

Date:	March 24, 2010
To:	Patricia Keegan, M.D. Director
	Division of Biologic Oncology Products (DBOP)
Through:	Mary Willy, PhD, Deputy Director Mary Willy 3/24/10
	Division of Risk Management (DRISK)
	Sharon R. Mills, BSN, RN, CCRP Sharon R. Mills 3/25/2010
	Senior Patient Labeling Reviewer, Acting Team Leader
	Division of Risk Management
From:	Melissa Hulett MSBA, BSN, RN Melissa Hulett 3/25/2010
	Patient Labeling Reviewer
	Division of Risk Management
Subject:	Addendum to DRISK Review of Patient Labeling (Medication Guide and Instructions for Use) dated March 15, 2010
Drug Name(s):	Epogen (epoetin alfa)
Application Type/Number:	BLA 103234/5166
Submission Date:	October 26, 2009
Applicant/sponsor:	Amgen Pharmaceuticals
OSE RCM #:	2009-2286

1 INTRODUCTION

This review is written as an addendum to DRISK's review of the Patient Labeling (Medication Guide and Instructions for Use) dated March 15, 2010 for Epogen (epoetin alfa). DRISK's review dated March 15, 2010 was 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 the Instructions for Use (IFU) for Epogen (epoetin alfa). The review of the Patient Labeling for Epogen (epoetin alfa) is also applicable to the Procrit (epoetin alfa) Patient Labeling.

Based on discussion with DBOP at the March 17, 2010 wrap-up meeting and follow up discussion with Dr. Keegan, revisions were made to the Instructions for Use for Epogen (epoetin alfa).

2 MATERIAL REVIEWED

- Draft Epogen (epoetin alfa) Instructions for Use (IFU) submitted on October 26, 2009 and provided to DRISK on March 4, 2010.
- DRISK Epogen (epoetin alfa) review of Instructions for Use (IFU) dated March 15, 2010.

3 RESULTS OF REVIEW

Based on discussion with Dr. Keegan, we have made revisions to the Epogen (epoetin alfa) Instructions for Use (IFU). Our annotated Instructions for Use is appended to this memo. No additional changes were made to the Medication Guide. Any additional revisions to the PI should be reflected in the MG and Instructions for Use.

Please let us know if you have any questions or wish to discuss the Instructions for Use further.

20 Page(s) of Draft Labeling has been Withheld in Full immediately following this page as B4 (CCI/TS)

CC list:

DBOP:
Patricia Keegan
Jeff Summers
Mona Patel

DMIHP:
Rafael Rieves

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

DDMAC:
Cynthia Collins
Wayne Amchin

DMIHP:
Ebla Ali Ibrahim

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. 3/17/10
Division of Drug Marketing, Advertising and Communications, CDER

Date: March 17, 2010

Re: **Epogen/Procrit (epoetin alfa)**
STN BL 103234/5166
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) for Epogen sent by electronic mail from DBOP on March 16, 2010. This version of the PI was sent to Amgen on March 10, 2010.

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 to DDMAC on January 11, 2010.

This draft product labeling converts the Epogen/Procrit 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.

DDMAC offers the following comments. We assume that these comments will also apply to the Procrit PI.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

(b) (4)

2 DOSAGE AND ADMINISTRATION

(b) (4)

5 WARNINGS AND PRECAUTIONS

(b) (4)

An increased incidence of thromboembolic reactions, some serious and life-threatening, occurred in patients with cancer treated with ESAs. [emphasis added]

3. *DDMAC Comment: Recommend including the word "adverse" prior to the word "reactions" to be consistent with the same sentence in the revised Aranesp PLR labeling.*

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

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

Memorandum

Date: March 16, 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 3/16/10

Subject: Epogen®/Procrit® (epoetin alfa) (Epogen/Procrit)
BLA 103234
DDMAC comments on proposed product labeling (PI)

DDMAC has reviewed the proposed PI for Epogen dated March 3, 2010, and submitted for consult on March 3, 2010. Our comments are based on the most version of the proposed PI sent via e-mail from DBOP on March 3, 2010. (This is the version that was sent to Amgen on March 3, 2010.)

DDMAC acknowledges that the proposed PI converts the existing Epogen 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 assume that any comments applied to Epogen would apply to the Procrit PI as well. We offer the following comments.

Highlights

Adverse Reactions

1. (b) (4)

   (b) (4) We recommend including these other common adverse reactions for consistency with the proposed PI or increasing the cutoff of the percent incidence.

2. "Zidovudine-treated HIV-infected Patients: (b) (4)

   (b) (4) We recommend including these other common adverse reactions for consistency with the proposed PI or increasing the cutoff of the percent incidence.

3. "Surgery Patients: (b) (4)

   (b) (4) We recommend including these other common adverse reactions for consistency with the proposed PI or increasing the cutoff of the percent incidence.

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 16, 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. 03-16-2010.
Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Re: **BLA 103234/5166: EPOGEN/PROCRIT (epoetin alfa for Injection)**
DDMAC label consult response: Epogen/Procrit Patient Instructions for Use

Background:

DDMAC has reviewed the following draft patient labeling for Epogen:

- Draft Medication Guide
  - document entitled "FDA Proposed Changes Epogen MedGuide Clean 3 4 2010"
  - revised March 4, 2010
  - accessed from March 4, 2010, e-mail from Mona Patel

- Draft Patient Instructions for Use
  - document entitled "PIU Epogen 2.4.2010 (eCTD 280)"
  - revised February 2, 2010
  - accessed from March 4, 2010, e-mail from Mona Patel

This review of the draft patient labeling for Epogen (epoetin alfa) is also applicable to the Procrit (epoetin alfa) draft patient labeling.

We offer the following comments on the draft patient labeling:

Medication Guide (MG)

DDMAC has no additional comments at this time.

Patient Instructions for Use (PIU)

1. Under "**What do I need to know about the different types of Epogen vials?**" the draft PIU states:

(b) (4)

However, the CONTRAINDICATIONS section of the draft PI (revised March 10, 2010; document entitled " FDA Proposed Changes Epogen PI Clean (Wrap Up) 3.10.2010") states:

(b) (4)

- Neonates, infants, pregnant women, and nursing mothers *[see Use in Specific Populations (8.1, 8.3, 8.4)]*

DDMAC Comment: *We recommend revising the draft PIU, so that the patient population contraindication for the multidose vial is included in the PIU. For example, two bullets could be added to the PIU section above, stating (1) "Do not take Epogen from multidose vials if you are pregnant or breast-feeding. Contact your healthcare provider." and (2) "Do not give Epogen from multidose vials to a baby or infant. Contact your child's healthcare provider."*

While we note that this information is also included in the draft Medication Guide for Epogen, we feel it is important to repeat this information in the PIU, given the potential for harm should the benzyl alcohol containing product be used in the contraindicated population.

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

Date:	March 15, 2010
To:	Patricia Keegan, M.D. Director
	Division of Biologic Oncology Products (DBOP)
Through:	Mary Willy, PhD, Deputy Director Mary Willy 3/15/10
	Division of Risk Management (DRISK)
	Sharon R. Mills, BSN, RN, CCRP Sharon R. Mills 3/15/2010
	Senior Patient Labeling Reviewer, Acting Team Leader
	Division of Risk Management
From:	Melissa Hulett MSBA, BSN, RN Melissa Hulett 3/15/10
	Patient Labeling Reviewer
	Division of Risk Management
Subject:	DRISK Review of Patient Labeling (Medication Guide and Instructions for Use)
Drug Name(s):	Epogen (epoetin alfa)
Application Type/Number:	BLA 103234/5166
Submission Date:	October 26, 2009
Applicant/sponsor:	Amgen Pharmaceuticals
OSE RCM #:	2009-2286

1 INTRODUCTION

Amgen Pharmaceuticals resubmitted a Prior Approval Supplement on October 26, 2009 in response to FDA's Complete Response Letter dated October 24, 2008. The submission addresses the PLR conversion of supplement BL STN 103234/5166.

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 the Instructions for Use (IFU) for Epogen (epoetin alfa). The review of the Patient Labeling for Epogen (epoetin alfa) is also applicable to the Procrit (epoetin alfa) Patient Labeling.

We plan to meet with DBOP on Wednesday, March 17, 2010 to discuss this review prior to sending to the Applicant.

2 MATERIAL REVIEWED

- Draft Epogen (epoetin alfa) Prescribing Information (PI) submitted October 26, 2009, revised by the Review Division throughout the current review cycle and provided to DRISK on March 4, 2010.
- Draft Epogen (epoetin alfa) Medication Guide (MG) submitted on October 26, 2009, revised by the review division throughout the review cycle and provided to DRISK on March 4, 2010.
- Draft Epogen (epoetin alfa) Patient Instructions for Use (IFU) submitted on October 26, 2009 and provided to DRISK on March 4, 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 is 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.

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CC list:

DBOP:
Patricia Keegan
Jeff Summers
Mona Patel

DMIHP:
Rafael Rieves

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

DDMAC:
Cynthia Collins
Wayne Amchin

DMIHP:
Ebla Ali Ibrahim

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: **March 2, 2010**

Re: **Comments on draft labeling for Epogen/Procrit (epoetin alfa)**
STN 103234/5166

We have reviewed the proposed label for the Complete Response resubmissions for Epogen/Procrit (FDA version dated 3/2/10) 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.

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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 301-796-9858

Maternal Health Team (MHT) Review

Date: March 1, 2010 **Date Consulted:** November 25, 2009

From: Richardae Araojo, Pharm.D. Richardae Aroj 3/1/2010
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 LLM 3/1/2010
Associate Director, Office of New Drugs
Pediatric and Maternal Health Staff

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

Drug: Epogen/Procrit (epoetin alfa); BLA 103234/5166

Subject: Pregnancy and Lactation Labeling

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

Consult Question: Please review Amgen's 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 Epogen and Procrit (epoetin alfa). This supplement proposed revisions to Epogen and Procrit prescribing information and reformatted the labeling according to the Physician's Labeling Rule (PLR).

Epogen and Procrit are erythropoiesis-stimulating agents (ESA) indicated for the treatment of anemia due to chronic renal failure, myelosuppressive cancer chemotherapy, zidovudine in HIV-infected patients, and reduction of allogeneic red blood cell transfusions in patients undergoing elective, non-cardiac, nonvascular surgery.

In June 2008, the Division of Medical Imaging and Hematology Products (DMIHP) and the Division of Biologic Oncology Products (DBOP) requested the MHT's review of published human data on Epogen exposure during pregnancy. The MHT conducted a literature search and reviewed the available published human data on epoetin alfa and human recombinant erythropoietin exposure during pregnancy (see review dated October 22, 2008). In addition, based on the information obtained, the MHT provided recommendations for labeling to DMIHP and DBOP (see review dated October 22, 2008).

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 labels.

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 Epogen/Procrit, FDA labeling issued in the Complete Response letter dated October 24, 2008, and the sponsor's proposed labeling in response to FDA's Complete Response letter. In addition, Table 1 provides the MHT reviewer's comments on the sponsor's proposed labeling.

Table 1. Epogen/Procrit (epoetin alfa)			
Current Approved Labeling	**Agency Labeling in Complete Response Letter dated October 24, 2008**	**Sponsor's Proposal**	**MHT Reviewer Comments**
Label not in PLR format.	(b) (4)		• Add nursing mothers to benzyl alcohol Contraindication based on Division proposed language in section 8.3.
			• Amgen Pregnancy Surveillance Program information added to Epogen label only, information should be added to Procrit label as well. • MHT received information Amgen submitted regarding their Pregnancy Surveillance Program (submitted to a different application).
			• Add nursing mothers to benzyl alcohol Contraindication based on Division proposed language in section 8.3.
Pregnancy Category C EPOGEN has been shown to have adverse effects in rats when given in doses 5 times the human dose. There are no adequate and well-controlled studies in pregnant women. EPOGEN should be used during pregnancy only if potential			• Add cross-reference to section 8.4 for detailed information on benzyl alcohol Contraindication. • Sponsor changed pregnancy exposures from (b) (4) to 33. MHT requested references from sponsor (on 12/23/09) to confirm revision.

Table 1. Epogen/Procrit (epoetin alfa)			
Current Approved Labeling	**Agency Labeling in Complete Response Letter dated October 24, 2008**	**Sponsor's Proposal**	**MHT Reviewer Comments**
benefit justifies the potential risk to the fetus. In studies in female rats, there were decreases in body weight gain, delays in appearance of abdominal hair, delayed eyelid opening, delayed ossification, and decreases in the number of caudal vertebrae in the F1 fetuses of the 500 Units/kg group. In female rats treated IV, there was a trend for slightly increased fetal wastage at doses of 100 and 500 Units/kg. EPOGEN has not shown any adverse effect at doses as high as 500 Units/kg in pregnant rabbits (from day 6 to 18 of gestation).	(b) (4)		Sponsor's response was received on 1/14/2010. • Not all published reports reviewed by MHT (see review dated October 22, 2008) indicated which human recombinant erythropoietin product was received during pregnancy. Therefore, the sponsor provided references for published reports that indicate Epogen or Procrit was administered during pregnancy. In addition, the sponsor provided information on post-marketing pregnancy exposures. Based on the sponsor's response, it is acceptable to change the human pregnancy exposures from (b) (4) to 33. In addition, the change in number of exposures does not change the data presented in the label. • Label should include a range for human equivalent exposures that correlate with animal doses presented in this section. • Amgen Pregnancy Surveillance Program information added to Epogen label only. MHT

Table 1. Epogen/Procrit (epoetin alfa)			
Current Approved Labeling	**Agency Labeling in Complete Response Letter dated October 24, 2008**	**Sponsor's Proposal**	**MHT Reviewer Comments**
		(b) (4)	recommends adding Amgen Pregnancy Surveillance Program information to Procrit label as well.
<u>Nursing Mothers</u> Postnatal observations of the live offspring (F1 generation) of female rats treated with EPOGEN			• Remove (b) (4) • Add cross-reference to section 8.4

Table 1. Epogen/Procrit (epoetin alfa)			
Current Approved Labeling	**Agency Labeling in Complete Response Letter dated October 24, 2008**	**Sponsor's Proposal**	**MHT Reviewer Comments**
during gestation and lactation revealed no effect of EPOGEN at doses of up to 500 Units/kg. There were, however, decreases in body weight gain, delays in appearance of abdominal hair, eyelid opening, and decreases in the number of caudal vertebrae in the F1 fetuses of the 500 Units/kg group. There were no EPOGEN-related effects on the F2 generation fetuses. It is not known whether EPOGEN is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when EPOGEN is administered to a nursing woman.	(b) (4)	(b) (4)	for detailed information on benzyl alcohol Contraindication.
Medication Guide **Dangers of giving Epogen to premature babies.** Epogen from multidose vials that contain benzyl alcohol should not be given to premature babies because it can cause death and brain damage. **What should I tell my healthcare provider before taking Epogen?**		**Medication Guide** (b) (4)	• Add nursing mothers to benzyl alcohol Contraindication based on Division proposed language in section 8.3 of label.

Table 1. Epogen/Procrit (epoetin alfa)			
Current Approved Labeling	**Agency Labeling in Complete Response Letter dated October 24, 2008**	**Sponsor's Proposal**	**MHT Reviewer Comments**
Epogen 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 Epogen may harm your unborn baby. • Are breast-feeding or planning to breast-feed. It is not known if Epogen passes into breast milk. • Women who do not have regular monthly menstrual periods may begin to have monthly periods while taking Epogen. Talk with your doctor about the possibility of pregnancy while taking Epogen.			

Epogen/Procrit Exposure during Pregnancy
Amgen's October 2009 submission proposed revising the number of epoetin alfa pregnancy exposures, presented in the Pregnancy section of labeling, from (b) (4) to 33. This revision was proposed based on Amgen's post-marketing experience as of May 2009, which includes:

- Two reports from clinical trials
- 13 reports from published literature
- 18 reports from physicians or other healthcare professionals.

The outcomes from these reports are presented in Table 2 below:

Table 2. Outcomes for Pregnancy Reports		
Outcome	**Reporting Period**	**Cumulative**
Normal Infant	4	8
Spontaneous abortion/miscarriage	0	0
Elective termination	0	0
Stillbirth	0	1
Abnormal Infant	1	7
Pregnancy ongoing/ unknown	4	17
Total	**9**	**33**

To confirm the sponsor's proposed revision, on December 23, 2009, the MHT requested Amgen submit references for all reports from published literature included in their safety database. The sponsor's response, received on January 14, 2010, provided references for five published reports of pregnant women, who were exposed to or likely exposed to Epogen or Procrit. In addition, the sponsor stated that all seven cases of an abnormal infant and one case of stillbirth were reported from published literature. The literature references cited by the sponsor are provided below:

1. Hou S, Orlowski J, Pahl M, Ambrose S, Hussey M, Wong D. Pregnancy in women with end-stage renal disease: treatment of anemia and premature labor. AM J Kidney Dis 1993 Jan; 21(1): 16-22.
2. Hussain S, Savin V, Piering W, Tomasi J, Blumenthal S. Phosphorus-enriched hemodialysis during pregnancy: Two case reports. Hemodialysis International 2005; 9: 147-52.
3. Johnson, J, Miller R, Samuels P. Bartter syndrome in pregnancy. Obstet Gynecol 2000 Jun; 95: 1035.
4. Santolaya-Forgas J, Meyer W, Gauthier D, Vengalil S, Duval J, Gottmann D. Transplacental passage of erythropoietin (EPO-alfa): A case control study. American Journal of Obstetrics and Gynecology 1997; 176: S83.
5. Yankowitz J, Piraino B, Laifer S, Frassetto L, Gavin L, Kitzmiller J, Crombleholme W. Erythropoietin in pregnancies complicated by severe anemia of renal failure. Obstet Gynecol 1992 Sept; 80: 485-88.

The MHT review dated October 22, 2008 (by R. Araojo), provided a summary of all reports listed above except Hussain 2005 and Johnson 2000. The literature report by Hussain and

colleagues describes two pregnant women with end-stage renal disease, both of whom developed hypophosphatemia after initiation of hemodialysis. Both women were treated with erythropoietin (brand product not specified) and other medications during pregnancy. One woman delivered a healthy boy at 31 weeks 5 days gestation, and no other infant outcomes were reported. The second mother delivered a 410g male infant by emergency cesarean section at about 25 weeks gestation due to "nonreassuring fetal heart tones and severe intrauterine growth retardation with reversed end-diastolic flow". The infant died one week after delivery.

Johnson and colleagues reported a 19 year old pregnant woman with Bartter syndrome who developed anemia and was treated with Epogen and other medications. The patient delivered a healthy girl by cesarean section at 34 weeks gestation with no signs of Bartter syndrome. No other infant outcomes were reported. The report also describes another case of Bartter syndrome during pregnancy however the patient was not exposed to Epogen or any erythropoietin product and no adverse infant outcomes were reported.

Reviewer comments:

- *Amgen lists the report by Johnson and colleagues as one in which an abnormal infant was born after exposure to Epogen in utero. However, the published report does not indicate that the infant had any congenital malformations or other adverse effects.*

- *The Hussain article reports two cases of exposure to an erythropoietin agent during pregnancy. Amgen states that these reports "could not be associated with an Amgen product or were not considered related to an Amgen product by the author". However Amgen entered into its safety database the one case of stillbirth reported in this article.*

- *Not all published reports reviewed by MHT (see review dated October 22, 2008) indicated which human recombinant erythropoietin product was received during pregnancy.*

- *Based on the sponsor's response, it is acceptable to change the human pregnancy exposures from (b)(4) to 33. In addition, the change in number of exposures does not change the data presented in the label.*

DISCUSSION AND CONCLUSIONS

For this review, the MHT made revisions to sections of the division's most recent revised draft of the sponsor's proposed Epogen/Procrit labeling related to pregnancy and lactation. In addition, the MHT reviewed the sponsor's response regarding the number of pregnancy exposures to Epogen/Procrit and confirmed that 33 pregnancy exposures, as proposed by the sponsor, are appropriate for labeling.

RECOMMENDATIONS

1. The MHT recommends the following language for the Highlights, Contraindications, Pregnancy, and Nursing Mothers sections of Epogen/Procrit labeling.

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------CONTRAINDICATIONS ----------

- Use of the multidose formulation in neonates, infants, pregnant women, and nursing mothers (4).

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

(b) (4)

4 CONTRAINDICATIONS

(b) (4)

- Neonates, infants, pregnant women, and nursing mothers [*see Use in Specific Populations (8.1, 8.3, 8.4)*]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

(b) (4)

(b) (4)

8.3 Nursing Mothers

(b) (4)

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, 2009

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: Epogen/Procrit (epoetin alfa) for injection, BLA 103234/5166/5010

Subject: Labeling Review

Materials Reviewed:

- Division of Pediatric Drug Development Memorandum, dated September 14, 2005 (regarding pediatric cancer indication)
- Sponsor Labeling submission dated October 23, 2009, revised labeling dated January 26, 2010

Consult Question: Review pediatric use information in Labeling/Medication Guide for PLR conversion of approved labeling.

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

INTRODUCTION

Epogen®/Procrtit® (epoetin alfa) Solution for intravenous or subcutaneous Use was approved June 1, 1989. Epoetin alfa is erythropoesis-stimulating agent (ESA) manufactured by recombinant DNA technology. The current approved indications are as follows (labeled indications are identical for Epogen and Procrit):

- Treatment of Anemia of Chronic Renal Failure Patients
- Treatment of Anemia in Zidovudine-treated HIV-infected Patients
- Treatment of Anemia in Cancer Patients on Chemotherapy
- Reduction of Allogeneic Blood Transfusion in Surgery Patients

Pediatric indications include:

- Pediatric Patients on Dialysis: Epogen/Procrit is indicated in infants (1 month to 2 years), children (2 to 12 years), and adolescents (12 to 16 years) for the treatment of anemia associated with CRF requiring dialysis.

- Pediatric Cancer Patients on Chemotherapy: Epogen/Procrit is indicated in patients 5 to 18 years old for the treatment of anemia due to concomitant myelosuppressive chemotherapy.

Although safety and effectiveness has not been established for the following indications, experience from published literature is reported in the Pediatric Use subsection of labeling:

- Pediatric Patients Not Requiring Dialysis: Published literature has reported the use of Epogen/Procrit in 133 pediatric patients with anemia associated with CRF not requiring dialysis, ages 3 months to 20 years.

- Pediatric Patients With HIV Infection Receiving Zidovudine: Published literature has reported the use of Epogen/Procrit in 20 zidovudine-treated, anemic, pediatric patients with HIV infection, ages 8 months to 17 years, treated with 50 to 400 Units/kg subcutaneously or intravenously 2 to 3 times per week. Increases in hemoglobin levels and in reticulocyte counts and decreases in or elimination of RBC transfusions were observed.

Amgen submitted a Prior Approval Labeling Supplement for Epogen®/Procrit® 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. In addition, Amgen converted adverse events to Adverse Drug Reactions. 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 Epogen®/Procrit® labeling.

BACKGROUND

As noted above, Epogen®/Procrit® (epoetin alfa) Solution for intravenous or subcutaneous Use was approved June 1, 1989. Erythropoesis-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 these 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.

REVIEW OF LABELING AND PMHS RECOMMENDATIONS
Proposed Epogen®/Procrit® Labeling dated January 26, 2010

The PMHS- Pediatric Team recommended labeling revisions are noted in reviewer comments.

The following sections of Epogen®/Procrit® labeling include pediatric-specific use information. PMHS notes that the information is identical for both products so for convenience we have included only information from the Epogen® labeling.

Highlights of Prescribing Information

----------DOSAGE AND ADMINISTRATION----------

- (b) (4) Patients: Initial dose: 50 to 100 Units/kg 3 times weekly (adults) and 50 Units/kg 3 times weekly (children on dialysis). Individualize maintenance dose. Intravenous route recommended for patients on hemodialysis (2.2).
- Cancer Patients on Chemotherapy: 40,000 Units weekly or 150 Units/kg 3 times weekly (adults); 600 Units/kg intravenously weekly (children ≥ 5 years) (2.4).

----------CONTRAINDICATIONS ----------

(b) (4)

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

- Pediatric Use: Safety and effectiveness have not been established in (b) (4) patients undergoing dialysis who are less than 1 month old, pediatric patients with cancer less than 5 years old, pediatric patients with (b) (4) not on dialysis, and pediatric patients with HIV infection (8.4).

Reviewer Comment: Highlights of Prescribing Information is specific to labeling in the PLR format. This section does not exist in the current approved labeling but captures the important pediatric use information.

2 DOSING AND ADMINISTRATION

(b) (4)

[redacted]

(b) (4)

Reviewer Comment: No revisions were made to pediatric dosing and administration information. Additional dosing safety information was added to the labeling which is acceptable.

4 CONTRAINDICATIONS

(b) (4)

Reviewer Comment: This information has been elevated from a Warning (current approved labeling) to a Contraindication. PMHS has provided, further information explaining the basis of the contraindication in subsection 8.4 Pediatric Use, to be consistent with the labeling for other products containing benzyl alcohol. In addition, PMHS – Maternal Health Team has recommended that nursing mothers be added to the contraindication statement:

> *"Neonates, infants, pregnant women, and nursing mothers [see Use in Specific Populations (8.1, 8.3, 8.4)]."*

6 ADVERSE REACTIONS
6.1 Clinical Trial Experience
Chronic Renal Failure Patients

Pediatric CRF Patients

In pediatric patients with CRF on dialysis, the pattern of adverse reactions was similar to that found in adults.

Reviewer Comment: The current approved labeling contains the following information: "Pediatric CRF Patients: In pediatric patients with CRF on dialysis, the pattern of most adverse events was similar to that found in adults. Additional adverse events reported during the double-blind phase in >10% of pediatric patients in either treatment group were: abdominal pain, dialysis access complications including access infections and peritonitis in those receiving peritoneal dialysis, fever, upper respiratory infection, cough, pharyngitis, and constipation. The rates are similar between the treatment groups for each event." Since the additional adverse events were similar to placebo, the proposed labeling revision is acceptable.

8 USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use

(b) (4)

Reviewer Comment: Remove the (b) (4) *from the Pediatric Use subsection and place in Pregnancy subsection. The statement should be revised as follows* (b) (4) *and PMHS recommends incorporating the standard pediatric benzyl alcohol language that is being added to labeling for all benzyl-alcohol containing products:*

> *"* (b) (4) *Benzyl alcohol has been associated with*

serious adverse events and death, particularly in pediatric patients. The "gasping syndrome," (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birthweight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse.

Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the "gasping syndrome", the minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birthweight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources."

<u>*Pediatric Patients on Dialysis:*</u> Epogen is indicated in infants (1 month to 2 years), children (2 to 12 years), and adolescents (12 to 16 years) for the treatment of anemia associated with CRF requiring dialysis. Safety and effectiveness in pediatric patients less than 1 month old have not been established [*see Clinical Studies (14.1)*]. The safety data from these studies are similar to those obtained from the studies of Epogen in adult patients with CRF [*see Warnings and Precautions (5) and Adverse Reactions (6.1)*].

Reviewer Comment: For clarity, combine pediatric age groups and revise the first sentence in the above paragraph to: "Epogen is indicated in pediatric patients, ages 1 month to 16 years of age, for the treatment of anemia associated with CRF requiring dialysis."

<u>*Pediatric Patients Not Requiring Dialysis:*</u> Published literature has reported the use of Epogen in 133 pediatric patients with anemia associated with CRF not requiring dialysis, ages 3 months to 20 years, treated with 50 to 250 Units/kg subcutaneously or intravenously, once weekly to 3 times weekly. Dose-dependent increases in hemoglobin and hematocrit were observed with reductions in RBC transfusion requirements.

<u>*Pediatric Cancer Patients on Chemotherapy:*</u> Epogen is indicated in patients 5 to 18 years old for the treatment of anemia due to concomitant myelosuppressive chemotherapy. Safety and effectiveness in pediatric patients less than 5 years have not been established *[see Clinical Studies (14.3)]*. The safety data from these studies are similar to those obtained from the studies of Epogen in adult patients with cancer *[see Warnings and Precautions (5) and Adverse Reactions (6.1)]*.

<u>*Pediatric Patients With HIV Infection Receiving Zidovudine:*</u> Published literature has reported the use of Epogen in 20 zidovudine-treated, anemic, pediatric patients with HIV infection, ages 8 months to 17 years, treated with 50 to 400 Units/kg subcutaneously or intravenously 2 to 3 times per week. Increases in hemoglobin levels and in reticulocyte counts and decreases in or elimination of RBC transfusions were observed.

Reviewer Comment: No content was added or deleted from the pediatric uses described above. The information on Pediatric Patients Not Requiring Dialysis was relocated as the second paragraph to keep the CRF information together. This revision is acceptable.

12 CLINICAL PHARMACOLOGY
12.3 PHARMACOKINETICS

The pharmacokinetic profile of Epogen in children and adolescents appeared similar to that of adults. Limited data were available in neonates. A study of 7 preterm, very low birth weight neonates and 10 healthy adults given intravenous erythropoietin suggested that distribution volume was approximately 1.5 to 2 times higher in the preterm neonates than in the healthy adults, and clearance was approximately 3 times higher in the preterm neonates than in the healthy adults.

Reviewer Comment: Epogen/Procrit is not approved in neonates. The pharmacokinetic information on neonates should be relocated to subsection 8.4 Pediatric Use so as not to infer an indicated use in the neonate population.

14 CLINICAL STUDIES
14.1 Chronic Renal Failure Patients

Pediatric Patients on Dialysis: The safety and efficacy of Epogen were studied in a placebo-controlled, randomized study of 113 children with anemia (hemoglobin ≤ 9 g/dL) undergoing peritoneal dialysis or hemodialysis. The initial dose of Epogen was 50 Units/kg intravenously or subcutaneously 3 times weekly. The dose of study drug was titrated to achieve either a hemoglobin of 10 to 12 g/dL or an absolute increase in hemoglobin of 2 g/dL over baseline.

At the end of the initial 12 weeks, a statistically significant rise in mean hemoglobin (3.1 g/dL vs. 0.3 g/dL) was observed only in the Epogen arm. The proportion of children achieving a hemoglobin of 10 g/dL, or an increase in hemoglobin of 2 g/dL over baseline, at any time during the first 12 weeks was higher in the Epogen arm (96% vs. 58%). Within 12 weeks of initiating Epogen therapy, 92.3% of the pediatric patients were RBC transfusion independent as compared to 65.4% who received placebo. Among patients who received 36 weeks of Epogen, hemodialysis patients required a higher median maintenance dose [167 Units/kg/week (n = 28) vs. 76 Units/kg/week (n = 36)] and took longer to achieve a hemoglobin of 10 to 12 g/dL (median time to response 69 days vs. 32 days) than patients undergoing peritoneal dialysis.

14.2 Cancer Patients on Chemotherapy
Study C2

Study C2 was conducted in 222 anemic patients ages 5 to 18 receiving chemotherapy for the treatment of various childhood malignancies. Randomization was stratified by cancer type

(b) (4)

(b) (4)

Sixty-nine percent of patients were white, 55% were male, and the median age of patients was 12 years (range: 5 to 18 years). (b) (4)

(b) (4)

There was no evidence of an improvement in health-related quality of life, including no evidence of an effect on fatigue, energy, or strength in patients receiving Epogen as compared to those receiving placebo.

Reviewer Comment: The pediatric study information was revised for clarity in the proposed labeling. Information was not added or deleted. The revisions are acceptable.

MEDICATION GUIDE

Who should not take Epogen?

(b) (4)

What are the possible side effects of Epogen?

- **Dangers of giving Epogen to newborns, infants, and pregnant women.** (b) (4)

Reviewer Comment: The information on not using the benzyl alcohol-containing multidose vials was new information added to the "Who should not take Epogen/Procrit" section of the Medication Guide. In addition, the information was revised to include infants and pregnant women in the section, "What are the possible side effects of Epogen/Procrit?" PMHS recommends revising, adding nursing mothers (as recommended by PMHS – Maternal Health

Team), and moving this information to the beginning of the Medication Guides and highlighting with bolding and a box, or other means for increased visibility of the information as follows:

(b) (4)

CONCLUSION

In summary PMHS – Pediatric Team recommends that the pediatric use information in Epogen®/Procrit® labeling be revised as previously discussed in this review.

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: Epogen®/Procrit® (epoetin alfa) (Epogen/Procrit)
BLA 103234
DDMAC comments on proposed product labeling (PI)

DDMAC has reviewed the proposed PI for Epogen/Procrit 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 13, 2010.

DDMAC acknowledges that the proposed PI converts the existing Epogen/Procrit 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

1. [redacted] (b) (4)

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

Adverse Reactions

1. (b) (4) [redacted]

   (b) (4) [redacted] We recommend including these other common adverse reactions for consistency with the proposed PI or increasing the cutoff of the percent incidence.

2. "Zidovudine-treated HIV-infected Patients: (b) (4) [redacted]

   (b) (4) [redacted] We recommend including these other common adverse reactions for consistency with the proposed PI or increasing the cutoff of the percent incidence.

3. "Surgery Patients: (b) (4) [redacted] "

   (b) (4) [redacted]. We recommend including these other common adverse reactions for consistency with the proposed PI or increasing the cutoff of the percent incidence.

Full Prescribing Information

Dosage and Administration

1. (b) (4) [redacted]

Patient Counseling Information

Information for Patients

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: 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. Cyn Coll 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 103234/5166: EPOGEN/PROCRIT (epoetin alfa for Injection)

Background:

DDMAC has reviewed the draft Medication Guides (MGs) for the erythropoiesis-stimulating agents (ESAs) Epogen and Procrit received on October 26, 2009, and located in the following electronic location:

- url: <\\cbsap58\M\eCTD_Submissions\STN103234\103234.enx>
- folder 0199, subfolder 1.14.1.3

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

We offer the following comments on the draft Medication Guides:

1. Under "**Patients with cancer:**" the MGs state:

(b) (4)

2. Under "**Who should not take Epogen [or Procrit]?**" the MGs state:

(b) (4)

3. Under "**What should I tell my healthcare provider before taking Epogen [or Procrit]?**" the MGs state:

- Are pregnant or planning to become pregnant. It is not known if Epogen [or Procrit] may harm your unborn baby.

Section 8.1 of the Epogen draft PI states that "Women who become pregnant during Epogen 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 Epogen MG? What about the Procrit MG? (The pregnancy registry is not referenced in the draft PI for Procrit.)*

4. Under (b) (4) the MGs state:

(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 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. CB 1/14/10
Division of Drug Marketing, Advertising and Communications, CDER

Date: January 14, 2010

Re: **Epogen/Procrit (epoetin alfa)**
STN BL 103234/5166
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 Epogen and offers the following comments. Please apply these comments to the draft Procrit labeling sent by electronic mail from DBOP on January 13, 2010, as the labeling changes for Epogen and Procrit are the same.

This draft product labeling converts the Epogen/Procrit 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.

23 Page(s) of Draft Labeling has been Withheld in Full immediately following this page as B4 (CCI/TS)

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

Name of Drug: Epogen® (epoetin alfa) and Procrit® (epoetin alfa)

Sponsor: Amgen Manufacturing Limited

Material Reviewed: Epogen® (epoetin alfa) and Procrit® (epoetin alfa) Highlights and Prescribing Information

OBP Receipt Date: January 4, 2010

Background:

Amgen has submitted a supplement to BLA 103234 to incorporate the Physician's Labeling Rule (PLR) conversion of the package insert for Epogen® (epoetin alfa) and Procrit® (epoetin alfa).

Label Reviewed:

Epogen® (epoetin alfa) and Procrit® (epoetin alfa) Prescribing Information-

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

Review

The changes to the prescribing information label for Epogen® (epoetin alfa) and Procrit® (epoetin 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 Epogen® (epoetin alfa) and Procrit® (epoetin 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".
   b. DOSAGE FORMS AND STRENGTHS (Epogen only)
      Please add the statement, [redacted] (b) (4) before the statement, "20,000 Units/2 mL and 20,000 Units/ 1 mL (3)".

2. Full Prescribing Information
   a. DOSAGE FORMS AND STRENGTHS (Epogen only)
      Please add the following statements to this section:
      i. [redacted] (b) (4) 2000 Units/ 1 mL, 3000 Units/1 mL, 4000 Units/1 mL, 10,000 Units/1 mL, and 40,000 Units/1 mL
      ii. [redacted] (b) (4) 20,000 Units/2 mL and 20,000 Units/1 mL

   b. DOSAGE AND ADMINISTRATION
      i. Section 2.6 Preparation and Administration
         1. Please revise the statement, "Do not shake." to [redacted] (b) (4)
         2. Please revise the statement, [redacted] (b) (4) to [redacted] (b) (4)

   c. 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)
      ii. Epogen only: Please correct the Citric acid amount listed for Single-dose 1 mL vials formulated with an isotonic sodium chloride/sodium phosphate buffer contain 40,000 Units of epoetin alfa from [redacted] (b) (4) to "0.0068 mg".

   b. HOW SUPPLIED/STORAGE AND HANDLING (Epogen Only)
      i. Please add the statement, "(in citrate-buffered formulation)" to the first line, "Single-dose, Preservative-free Vial".

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

Label attached

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

Memorandum

Date: October 24, 2008

From: Monica Hughes, M.S., Lead, Regulatory Health Project Manager
DBOP/OODP/OND/CDER/FDA

Subject: Patient Labeling: BL STN 103234/5166 (Epogen/Procrit) and 103951/5173 (Aranesp)

We note that under separate supplements that we are currently reviewing, BL STN 103234/5195 and 103951/5195, the patient package insert has been converted to a medication guide and patient instructions for use. Therefore, we reject all changes to the proposed package insert submitted under these supplements and are attaching the current versions of the medication guide and patient instructions for use documents as the current versions of the patient labeling.

21 Page(s) of Draft Labeling has been Withheld in Full immediately following this page as B4 (CCI/TS)

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

Maternal Health Team Review

Date: October 22, 2008 **Date Consulted:** October 16, 2008

From: Richardae Araojo, Pharm.D. Richardae Ary 10/22/08
Regulatory Reviewer, Maternal Health Team (MHT)
Pediatric and Maternal Health Staff

Through: Karen Feibus, MD
Team Leader, Maternal Health Team (MHT) 10/22/08
Pediatric and Maternal Health Staff

Lisa Mathis, MD LM 10/22/08
Associate Director, Pediatric and Maternal Health Staff

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

Drug: Epogen (epoetin alfa); STN 103234/5166

Subject: Pregnancy and Nursing Mothers Labeling

Materials Reviewed: Pregnancy and Nursing Mothers subsections of Epogen labeling.

Consult Question: Please review the Pregnancy and Nursing Mothers subsections of labeling.

INTRODUCTION

On December 26, 2007, Amgen, Inc. submitted a supplemental application for Epogen (epoetin alfa) solution for injection. In June 2008, the Division of Medical Imaging and Hematology Products (DMIHP) requested that the Maternal Health Team (MHT) review the Pregnancy and Nursing Mothers subsections of Epogen labeling. After reviewing MHT's recommendations, DMIHP requested a formal review of the human data on the use of Epogen during pregnancy, but did not provide a formal timeline. In the interim, hematology products were transferred to the Division of Biologic Oncology Products (DBOP). On October 10, 2008, the Safety Endpoints and Labeling Development (SEALD) Team forwarded DBOP's draft labeling for Epogen to MHT for review. As per DBOP's request, this review summarizes the published literature on Epogen use during pregnancy and our recommended labeling revisions.

BACKGROUND

Epoetin alfa is a human recombinant erythropoiesis-stimulating agent indicated for the treatment of anemia caused by chronic renal failure, zidovudine treatment, or chemotherapy for non-myeloid malignancies. It is also indicated for reduction of allogeneic red blood cell transfusions during surgery in anemic patients.

In the clinical setting, epoetin alfa is used in pregnant women with anemia alone or anemia associated with severe renal disease and other hematologic disorders. The remainder of this review will summarize published data on the use of epoetin alfa in pregnant women followed by labeling recommendations based on these data.

REVIEW OF DATA

- Published data on the use of recombinant human erythropoietin in pregnant patients
- Draft labeling

1. Review of Published Data

The Maternal Health Team performed a PubMed search with the following terms:

- Pregnancy and epoetin alfa
- Pregnancy and epoetin
- Epoetin and fetus
- Recombinant human erythropoietin and pregnancy

Table 1 below summarizes the case reports and small cohort studies identified which contain information on outcomes of pregnancies treated with rHuEPO.

Table 1: Summary of published literature on pregnant women treated with human recombinant erythropoietin (rHuEPO)					
Article	**Study Type**	**# Subjects**	**Indication for Treatment**	**rHuEPO Dose**	**Clinical Outcomes and Adverse Events**
Renal Failure					
Hou et.al. (1993)	Case report	5	End Stage Renal Disease	**Case 1:** 2000U 3x/week during first trimester (duration of treatment not provided) **Case 2:** 2000U 3x/week to ~9000U throughout pregnancy. **Case 3:** 2000U 3x/week at 15 weeks gestation (cont. on next page)	**Case 1:** Patient had history of renal disease and multiple congenital anomalies. Pregnancy complicated by vaginal bleeding, renal complications, oligohydramnios, and premature labor. Patient treated with dialysis, packed red blood cells, terbutaline, indomethacin, and other medications to control preterm labor and renal disease. At 33 weeks, 2230 g male infant delivered by cesarean. Apgar scores of 7/7; Hct = 57%. Infant had pectus excavatum and hypospadius and developed apnea. Required intubation for 1 week. **Case 2:** Patient treated with dialysis, prednisone, labetolol, packed red blood cells, and iron throughout pregnancy. At 23 weeks gestation, patient had polyhydramnios and was treated for preterm labor with terbutaline, indomethacin, magnesium sulfate, and nifedipine. At 34 weeks gestation, fetal ultrasound showed right atrial and ventricular enlargement. At 34 weeks gestation, 1942 g male infant delivered. Apgar scores of 9/9. Infant hematocrit was 68% and reticulocyte count was 9%. Infant had mild respiratory distress, jaundice, and two cyanotic bradycardic episodes. An echocardiogram showed dilated right ventricle and mild tricuspid regurgitation. Follow-up echocardiogram normal at one month of age. **Case 3:** At 15 weeks gestation, patient started on rHuEPO. Hematocrit increased from 24.8% to 34%. Mild polyhydramnios occurred. At 35 weeks gestation a female infant weighing 2040g was delivered. Infant had Apgar scores of 9/9. The infant had normal renal function; a distended renal pelvis was attributed to increased osmotic load to the fetal kidneys. No other abnormalities noted.

Table 1: Summary of published literature on pregnant women treated with human recombinant erythropoietin (rHuEPO)					
Article	**Study Type**	**# Subjects**	**Indication for Treatment**	**rHuEPO Dose**	**Clinical Outcomes and Adverse Events**
Hou et.al. (1993) **continued**				**Case 4:** 2000U 3x/week prior to conception and at increasing doses through out pregnancy (max dose was 16000U) **Case 5:** 4000U 3x/week, increased to 6000U during pregnancy.	**Case 4:** Patient with renal failure complicated by severe renal osteodystrophy. Pregnancy diagnosed at 17 weeks gestation. Patient received dialysis through out pregnancy. At 24 weeks gestation, a premature female infant was delivered weighing 560g with 1 and 5 minute Apgar scores of 3 and 5, respectively. Infant died at 10 hours of age with respiratory distress and pneumothorax. **Case 5:** Patient with end-stage renal disease secondary to systemic lupus erythematosus. Patient received dialysis and iron during pregnancy. Pregnancy complicated by severe hypertension and urinary tract infections. Ultrasound showed severe fetal growth retardation. Intrauterine fetal death at 27 weeks gestation followed by induced delivery of 350g stillborn male infant with no congenital anomalies noted.
Kashiwagi, et.al. (2002)	Case report	1	Anemia and renal failure in pregnancy	20000U/week from 32 – 34 weeks gestation with parenteral iron	rhEPO administered at 32 weeks gestation for worsening renal function and intrauterine growth retardation. Hematocrit increased by 0.4% daily and hemoglobin increased from 8.6 to 10.3 g/dl). Cesarean delivery at 34 weeks gestation for worsening maternal preeclampsia and renal function. Neonatal Apgar scores and arterial pH were normal. Infant weighed 1590g and hematocrit was 50%. No congenital abnormalities observed. Maternal blood pressure and renal function stabilized with further treatment postpartum.
Mátyus et.al. (1996)	Case report	2	Severe anemia of chronic renal failure	**Case 1:** 25 weeks gestation: 2000 U (38 U/kg) 3x/week with parenteral iron. 28 weeks gestation: 4000U 3x/ week. 30 weeks gestation: 2000U once a week until delivery. **Case 2:** 2000U (42U/kg) 3x/week with parenteral iron at 20 weeks gestation. At 26 weeks, 2000U twice a week.	**Case 1:** Anemia resolved. A 2100g infant was delivered at 39 weeks gestation. Infant had Apgar score of 10 at 5 minutes. No postpartum or neonatal problems occurred. **Case 2:** After 9 weeks of rhEPO treatment, patient developed preeclampsia and edema. At 31 weeks gestation, 1280g infant delivered by cesarean. Apgar score of 8 at 5 minutes. After delivery, maternal blood pressure and volume status normalized. Renal function improved gradually over the next few months.

Table 1: Summary of published literature on pregnant women treated with human recombinant erythropoietin (rHuEPO)					
Article	**Study Type**	**# Subjects**	**Indication for Treatment**	**rHuEPO Dose**	**Clinical Outcomes and Adverse Events**
Kontessis et. al. (1995)	Case report	1	Lupus nephritis and severe anemia	2000U (110U/kg) 3x/week and ferrous sulfate 200mg three times a day. At 25 weeks gestation dose increased to 12,000U/week	At 33 weeks gestation, patient had a mild increase in blood pressure that was treated with atenolol. Anemia and blood pressure remained stable. At 35 weeks gestation, 3200 g male delivered by cesarean. Apgar scores were 8 and 10 at 1 and 5 minutes, respectively. Infant's initial H/H= 16.1 g/dL /50.7%. Normal WBCs and platelets. Mild hyperbilirubinemia from day 2 to day 4 of life. Infant was discharged home 11 days after delivery.
Scott et.al. (1995)	Case report	2	Severe anemia of chronic renal failure	**Case 1:** 10000U (143U/kg) 3x/week 32 – 36 weeks gestation. Stopped for Hct = 33%. **Case 2:** 4500U (45U/kg) 3x/week started at about 23 weeks gestation	**Case 1:** After treatment with rHuEPO, maternal Hct and reticulocyte count improved. Maternal blood pressure remained stable. A healthy 3160 g female infant delivered at 38 weeks gestation. No neonatal adverse events. **Case 2:** Patient had chronic hypertension treated with labetolol throughout pregnancy. After 10 days of rHuEPO treatment at 28 weeks gestation, patient developed severe preeclampsia. A healthy 1080 g preterm female infant delivered by cesarean. No adverse neonatal effects were noted. Patient continued on rHuEPO and labetolol postpartum; blood pressure and anemia improved.
McGregor et.al. (1991)	Case report	1	Reflux Nephropathy and anemia	Prior to conception: 2000U 2x/week and ferrous sulfate. Dose increased to 4000U at 18 weeks gestation.	Patient experienced polyhydramnions at 25 weeks of pregnancy and ultrasound revealed poor fetal growth. Patient received dialysis, nifedipine and atenolol during pregnancy. Severe fetal growth retardation noted at 31 weeks gestation. A 780 g preterm female infant was delivered by cesarean with Apgar scores of 2 and 6 at 1 and 5 minutes, respectively. Assisted ventilation was needed during the first 24 hours. The infant had mixed intrinsic and extrinsic coagulopathy and thrombocytopenia. Infant was discharged home at 66 days of life.

Table 1: Summary of published literature on pregnant women treated with human recombinant erythropoietin (rHuEPO)					
Article	**Study Type**	**# Subjects**	**Indication for Treatment**	**rHuEPO Dose**	**Clinical Outcomes and Adverse Events**
Yankowitz, et.al. (1992)	Case report	3	Anemia of renal failure	**Case 1:** 3000U/week (50U/kg/week) at 20 weeks gestation. Dose increased to 4000U/week at 30 weeks gestation. **Case 2:** 50U/kg 3x/week (9000U/week) at 26 weeks gestation. **Case 3:** 2000U 3x/week at 14 weeks gestation. At 16 weeks, dose increased to 4000U 3x/week. Dose decreased to 4000U 2x/week at about 18 weeks gestation.	**Case 1:** Patient received rHuEPO throughout pregnancy in increasing doses. Hematocrit gradually increased. Polyhydramnios noted at 32 weeks gestation. A 2570g male infant was delivered with Apgar scores of 8/8. The infant's cord Hct = 43.5%. Normal platelets and WBCs. Neonatal problems included mild hyperbilirubinemia and supplemental oxygen requirement. The infant was discharged after 11 days and was doing well at 3 months. **Case 2:** Patient with history of type 1 diabetes, hypertension, retinopathy, neuropathy, gastroparesis, and a previous 30-week stillbirth with cardiac defects. After rHuEPO treatment, patient's hematocrit improved. At 32 weeks, patient had worsening renal function, polyhydramnios, and preeclampsia. Labor induced. A 2020g male infant was delivered with 1 and 5 minutes Apgar scores of 4 and 7, respectively. The infant's cord Hct = 55.8%, platelet level was 187,000 µL, WBC 15,100 µL, and cord erythropoietin was 62 mIU/ml (normal <19). Infant had hypoglycemia and hyperbilirubinemia. Infant discharged at 2 weeks of age. **Case 3:** Twin gestation. Patient hematocrit level improved after rHuEPO treatment. At 35 weeks gestation, labor induced for worsening renal function. The patient delivered a 2220g female with Apgar scores of 4 and 8, and a 2410g male with Apgar scores of 2 and 5. Infants had normal platelets and hematocrits of 48.4% (female) and 53.1% (male). At 7 months of age, twins developing normally.
Hematologic Disorders					
Tan, et.al. (2007)	Case report	1	Sickle cell disease and anemia	20,000 units and intravenous iron	Patient experienced three sickling crises, which caused a decrease in hemoglobin. rhEPO and intravenous iron administered, and the patient's hemoglobin stabilized. At 38 weeks, a 2400g female infant was delivered by cesarean. No adverse effects in the infant.

Table 1: Summary of published literature on pregnant women treated with human recombinant erythropoietin (rHuEPO)					
Article	**Study Type**	**# Subjects**	**Indication for Treatment**	**rHuEPO Dose**	**Clinical Outcomes and Adverse Events**
Bencaiova, et.al. (2006)	Prospective cohort study	19	Heterozygous hemoglobino-pathy and anemia	Treatment was divided into two phases: Low dose phase - 3 doses 10,000U administered with intravenous iron sucrose. High dose phase - in patients showing a poor response to low dose rhEPO, the dose was increased to 20,000 U. Doses were adjusted based on hemoglobin (Hb) level.	19 women enrolled: 13 had ß-thalassemia trait, 2 had a-thalassemia trait, 3 had the sickle cell trait, and 1 had heterozygous hemoglobinopathy E. Mean gestational age at the start of rHuEPO therapy was 28 weeks; mean gestation age at end of therapy was 32 weeks. All patients showed stimulation of erythropoiesis with an increase in hemoglobin. Thirteen patients had a good response to therapy (mean Hb increase 1.6 $\pm$ 0.5 g/dl). Six patients showed resistance to rhEPO (mean Hb increase 0.5 $\pm$ 0.5 g/dl). These patients were treated in the high dose phase with rHuEPO 320.9 $\pm$ 61.2 U/kg body weight. There were no thromboembolic complications or blood pressure increases, and no allergic reactions attributable to parenteral iron or rhEPO. There were no detectable adverse effects on the fetus or newborn based on birth weight and first neonatal examination. Patient response to rhEPO varied widely in anemic pregnant patients with heterozygous hemoglobinopathy and resistance was observed in patients with ß-thalassemia trait originally from the Mediterranean region.
Donato, et al. (2003)	Case report	1	Anti-Di^b	600U/kg, twice weekly at ~20 weeks gestation.	To ensure an adequate supply of compatible RBCs for a possible exchange transfusion, the mother was prepared for RBC collections with rHuEPO. After four doses and two blood collections, 900 mL of compatible whole blood was obtained. The infant was delivered by cesarean at 37 weeks gestation. The infant's RBCs were group AB, D+, Di(b+). At delivery, the infant's total bilirubin concentration was 2.3 mg/dL and Hb was 16.9 g/dL. Seventy-two hours after birth, the infant began phototherapy for mild hyperbilirubinemia. The infant was discharged 9 days after birth without complications and with a bilirubin concentration of 7.1 mg/dL. The mother experienced no adverse events from rHuEPO.
Lialios et al. (2000)	Case report	1	ß-thalassemia intermedia	rHuEPO 200IU/kg every other day for 4 weeks combined with iron and folic acid.	After rHuEPO therapy initiated, patient's hematologic levels improved. A healthy 2520 g male infant was delivered by cesarean.

Table 1: Summary of published literature on pregnant women treated with human recombinant erythropoietin (rHuEPO)					
Article	**Study Type**	**# Subjects**	**Indication for Treatment**	**rHuEPO Dose**	**Clinical Outcomes and Adverse Events**
Santolaya-Forgas et al. (1999)	Case report	1	Js^b allo-immunization	600U/kg, biweekly at 18 weeks gestation. Patient received 25 doses during pregnancy.	Patient had Js^b alloimmunization and twin pregnancy. At 18 weeks gestation, patient started on rHuEPO treatment to prevent anemia secondary to serial blood donations for fetal transfusions. Due to decreased fetal hematocrit, fetal blood transfusion was performed at 18 weeks. No complications occurred; however, 5 days after the procedure, twin A died. Twin B continued to receive intravascular transfusions at 2-3 weeks intervals. At 37 weeks gestation, cesarean performed. Infant weighed 2723g and had Apgar scores of 6 and 8 at 1 and 5 minutes, respectively. Infant received one additional transfusion after birth and was discharged home on day 8 of life.
Anemia					
Sifakis et al. (2001)	Prospective cohort study	26	Iron deficiency anemia	150 IU/kg 3x/week and 100 mg parenteral iron daily, for 4 weeks.	Study enrolled 26 pregnant women ineffectively treated for anemia with iron supplementation alone for at least 8 weeks. Nineteen of the 26 women (73%) showed a quick response to treatment, with Hb reaching normal levels within 2 weeks. Five women (19.2%) had no significant increase in Hb levels. Hb concentration decreased in 2 women (7.6%), and they required blood transfusion. Two 35-year-old pregnant women, both in the third trimester, experienced hypertension during treatment, which was managed with 250 mg of methyldopa three times daily. In 1 case, an allergic reaction caused an early termination of treatment. Two other women had a single episode of face redness, tachycardia and ephidrosis during IV iron administration. Fetal IUGR occurred in 1 case with prolonged maternal Hb levels <8 g/dl. This patient required blood transfusion in the 30th week of pregnancy, developed preterm labor at 33 weeks and delivered without neonatal complications. All other pregnancy outcomes were reported as normal. Hematological parameters in the neonates (Hb, red blood cells indices, and reticulocytes count) were normal. There were no signs of adverse effects on the neonates associated with maternal treatment.

Table 1: Summary of published literature on pregnant women treated with human recombinant erythropoietin (rHuEPO)					
Article	**Study Type**	**# Subjects**	**Indication for Treatment**	**rHuEPO Dose**	**Clinical Outcomes and Adverse Events**
Harris, et al. (1996)	Case report	1	Hypoproliferative anemia without renal disease	100U/kg 3x/week at 18 weeks gestation (dose increased through out pregnancy as needed, maximum dose administered not provided).	Infertility patient who conceived with leuprolide acetate and menopausal gonadotropin therapy. She developed anemia (hemoglobin 8.5 g/dL) in early pregnancy. Laboratory findings showed hypoproliferative marrow and low serum erythropoietin level. Patient was treated with rHuEPO from 18 weeks gestation until delivery. The rHuEPO dose was adjusted to maintain a hemoglobin level of 10.5 to 11.5 g/dL. The pregnancy was otherwise uncomplicated. Maternal blood pressure remained normal and fetal growth was normal. At 38.5 weeks gestation, the patient delivered a healthy, 3515 g, female infant. The mother's pre-delivery hemoglobin level and hematocrit were 12 g/dL and 35.5%, respectively, and her post-delivery hemoglobin level and hematocrit were 8.2 g/dL and 23.7%, respectively. The fall in hemoglobin was secondary to acute blood loss at delivery, and the patient remained hemodynamically stable without transfusion. The newborn had an uncomplicated hospital course with a normal hemoglobin level of 20.6 g/dL and a hematocrit of 59.9%.
Breymann et al. (1995)	Prospective cohort study	11	Severe iron deficiency anemia	rHuEPO 300U/kg and saccharated iron 200mg once weekly (started at gestational age over 20 weeks).	Eleven anemic pregnant women were treated once weekly until a hemoglobin value of 11.0 g/dl was reached. Eight of the 11 patients showed an immediate response (average increase in hemoglobin was of 0.7 g/dl per week). The average treatment period for this group was 17 days. Three patients did not respond immediately to treatment but showed a delayed pattern of hemoglobin increase (average weekly hemoglobin increase was 0.3 g/dl) and treatment was continued over 28 days. These patients also had lower serum ferritin values, low transferrin saturation and a lower reticulocyte count before treatment. There were no major side effects observed during the study (no blood pressure increases or anaphylactic reactions). Newborn hemoglobin levels, hematocrit and reticulocyte counts were all within the normal range. No negative influence on the fetal outcome was detected. The authors concluded that rhEPO and parenteral iron is effective in stimulating erythropoiesis and in treating certain pregnancy anemias. They hypothesized that poor response to treatment may be due to insufficient iron supplementation during therapy with rhEPO or factors that inhibit erythropoiesis during pregnancy, like undetected infections.

Discussion of Published Data

The 76 subjects presented in Table 1 received recombinant human erythropoietin in different clinical scenarios. Women with alloimmunization received treatment to permit repeated maternal blood donation for fetal transfusion. Most of the other subjects received treatment for medical conditions associated with chronic anemia potentially exacerbated by pregnancy.

Thirty-eight patients received a combination of rHuEPO and iron therapy (oral or parenteral) for the treatment of iron deficiency anemia during pregnancy. Among these subjects, two women of advanced maternal age developed pregnancy induced hypertension and one subject had preterm labor and delivery. Fetal intrauterine growth restriction (IUGR) occurred in one case with prolonged maternal Hb levels <8 g/dl.

Among 21 women with a hemoglobinopathy, there were no adverse pregnancy or neonatal complications. Among two women with alloimmunization that induced fetal anemia, there was one fetal death and one case of neonatal jaundice in an infant that received blood transfusions in utero.

Fifteen pregnant women with underlying renal disease received rHuEPO for chronic anemia and experienced a higher rate of pregnancy complications. Four women were treated for chronic hypertension and two experienced exacerbation of their renal disease. Five women experienced preterm labor and delivery. An additional five women were delivered preterm due to preeclampsia (four patients) and or IUGR (three patients). Other pregnancy and neonatal complications included:

- Type 2 Diabetes Mellitus (n=1)
- Maternal congenital renal disease (n=1)
- Fetal death (n=1)
- Neonatal death at 24 weeks gestation (n=1)
- Infant born with pectus excavatum and hypospadias (n=1)
- Polyhydramnios (n=4)
- Oligohydramnios (n=1)
- Vaginal bleeding (n=1)
- Neonatal hyperbilirubinemia (n=3).

Polyhydramnios, intrauterine growth restriction, and prematurity occur more frequently in women with chronic renal disease. It is not possible to determine causality between these pregnancy outcomes and exposure to rHuEPO in utero due to multiple confounding factors such as underlying maternal conditions, other maternal medications, and gestational timing of exposure. While these postmarketing data do not reliably estimate the frequency or absence of drug-associated adverse outcomes, they do provide useful human data for health care practitioners counseling pregnant women about the risks and benefits of therapy with recombinant human erythropoietin.

2. Review of Division's Draft Pregnancy and Nursing Mothers Labeling

Highlights

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

(b) (4)

[redacted]

8.1 Pregnancy

Pregnancy Category C

(b) (4)

[redacted]

8.3 Nursing Mothers

(b) (4)

[redacted]

RECOMMENDATIONS

Provided below are MHT's recommended revisions to the sponsors' proposed labeling. Appendix A of this review provides a track changes version of labeling that highlights all changes made.

The MHT would greatly appreciate if the DBOP Pharm Tox team could calculate the approximate or actual multiples of human dose/exposure for the animal doses in the Pregnancy subsection of the label. Since the labeling regulations require animal doses be expressed in

human dose/exposure multiples, we recommend including an explanatory statement in the animal data paragraph if these dose/exposure multiples cannot be calculated. These dose multiples are more understandable and meaningful for clinicians.

Highlights – no changes made

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

(b) (4)

8.1 Pregnancy

<u>Pregnancy Category C (single dose formulation only)</u>

(b) (4)

8.3 Nursing Mothers

(b) (4)

[redacted]

CONCLUSIONS

While the Proposed Pregnancy and Lactation Labeling Rule, published May 2008, is in the clearance process, the MHT is structuring the Pregnancy and Nursing Mothers label information in a way that is in the spirit of the Proposed Rule while still complying with current regulations. The goal of this restructuring is to make the pregnancy and lactation sections of labeling a more effective communication tool for clinicians.

The MHT's recommended labeling for Epogen is provided on pages 12-13 of this review.

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Division of Drug Marketing,
Advertising, and Communications

Internal Consult

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

To: Monica Hughes, Lead Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products

From: Carole C. Broadnax, R.Ph., Pharm.D. CB 10/20/08
Division of Drug Marketing, Advertising and Communications, CDER

Date: October 20, 2008

Re: **Epogen/Procrit (epoetin alfa)**
STN BL 103234/5166
Comments on draft labeling

In response to your Request for Consultation dated October 9, 2008, we have reviewed the draft labeling sent by electronic mail on October 9, 2008, for Epogen and offer the following comments.

Comments are included in the attached draft labeling as tracked changes.

19 Page(s) of Draft Labeling has been Withheld in Full immediately following this page as B4 (CCI/TS)

Division of Medical Imaging and Hematology Products

Sponsor	Amgen
Drug Name, Generic (Trade)	Epoetin alfa (Epogen/Procrit)
Indications	Anemia due to Chronic Renal Failure Chemotherapy, Zidovudine; Reduction of Allogeneic Blood Transfusion in Surgery Patients
Medical Officer	Minh-Ha Tran, D.O. 10/20/08
Acting Team Leader	Kassa Ayalew, M.D. 10/20/08
Division Director	Dwaine Rieves, M.D., Division Director
Application	BLA103234/5166 Epoetin alfa (Epogen)
Filing Date	December 20, 2007
Submission	BLA103234/5166 Epoetin alfa (Epogen) (SN 0096) Justification for Labeling Changes in Converting to PLR format; PLR materials
Item	Medical Officer Review of PLR Submission

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1. Background

On on December 20, 2007, Amgen submitted a supplemental BLA (SN 0096) to update a Physician Labeling Rule (PLR) supplement to the Division of Medical Imaging and Hematology Products (DMIHP) .

Epoetin alfa (Epogen), manufactured by Amgen is currently marketed worldwide under the trade names EPOGEN® (Amgen) and PROCRIT® (J&J).

FDA approved indications for Epoetin alfa (Epogen) include:

1) Treatment of anemia due to chronic renal failure (CRF)
2) Treatment of anemia due to zidovudine treatment in patients with HIV
3) Treatment of anemia due to concomitant chemotherapy
4) Reduction of allogeneic blood transfusion in surgery patients.

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). Reviewed material from the labeling submission included:

- Cover Letter
- Cross Reference to Other Applications
- Request for a Waiver (of the half-page limit for the Highlights section)
- Annotated Draft Labeling Text
- Proposed Physician Package Information
- clinical-overview-adr.pdf
    - i. containing justification for the submitted Adverse Reaction Tables including a summary of 5 randomized, placebo-controlled trials
- hiv-onc-surgery-adr.pdf
    - i. containing justification for the submitted AR Tables including a summary of ADR information for clinical studies involving HIV, Surgery, and Oncology patients treated with Epogen.

From the DMIHP/Non-cancer indications standpoint, the PLR submission contained a revised analysis of Adverse Reaction rates. The following quote from that document summarizes sponsor methodology in formulating the revised adverse reaction rates:

> "The FDA ADR Guidance suggests that 'The data in the listing of common adverse reactions should be derived from placebo-controlled and/or dose-response studies if these data are available and the databases are sufficiently large to be informative.'
> In agreement with this guidance, Amgen and J&JPRD reviewed adverse events from the randomized, double-blind, placebo-controlled studies included in the initial Epoetin alfa Biologics License Application (BLA) (J&JPRD Studies G86-011, EP86-001, EP86-004, H87-054, and Amgen Study 8701). Studies G86-011 and H87-054 enrolled subjects with CRF who were not receiving dialysis and Studies EP86-001, EP86-004 and 8701 enrolled subjects with CRF receiving dialysis. Of note, the current analyses utilized final adverse event data from the completed studies; whereas the adverse reaction

information in the current USPI is based upon interim data from these studies, which were ongoing at the time of the BLA.

Separate analyses of the nondialysis and dialysis studies revealed no major study-to study differences in study design, patient population, and adverse events rates.Therefore, all 5 studies were combined for analysis. The exception was vascular access thrombosis, which is restricted to the dialysis population, and was evaluated using combined data from the 3 dialysis studies only."

3. Review of Proposed Adverse Reaction Rates

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 randomized, placebo-controlled trials: EPO/e8701, JNJ/86-001, 86-004, 86-011, 87-054. This data was submitted in tabular form in the document clinical-overview-adr.pdf.

Demographics

A total of 454 subjects (279 Epoetin alfa, 175 placebo) from 5 randomized, double-blind, placebo-controlled clinical studies were included in the analyses.

The mean (range) age of subjects in the 5 studies was 52 (20 to 80) years.
Two hundred fifty-four subjects (56%) were men. The racial distribution was as follows: 341 subjects (75%) were white, 86 subjects (19%) were black, 7 subjects (2%) were Asian, 15 subjects (3%) were other, and racial information was missing for 5 subjects (1%). Two hundred forty-four subjects (54%) were receiving dialysis and 210 subjects (46%) were not receiving dialysis.

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.

Proposed Adverse Events Table

Table 1 depicts the proposed modifications superimposed on the currently approved Adverse Event table for CRF patients.

Table 1: Proposed Adverse Reaction Table (CRF) Based on Previously Approved Adverse Event Table

(b) (4)

The proposed adverse reactions for the modified table are:

(b) (4)

Reviewer Analysis of Submitted Trial Data for Adverse Events in Chronic Renal Failure Patients

In reviewing the rationale of the sponsor, the table containing adverse event data from all 5 reviewed trials was examined in the following manner:

1. All events occurring in < 1% of Epogen-treated subjects were removed
2. The remaining events were grouped into a new table (events > 1%)
3. From this table, all events occurring more frequently in the placebo group were removed
4. The remaining events were grouped into a new table (EPO>PBO)
5. From this table, events that did not appear to be biologically plausible in relation to the mechanism of action of the drug were removed
6. The remaining events were grouped into a new table which appears below:

Table 2: Reviewer Constructed Table Based Sponsor Submitted Adverse Event Data from 5 Trials

preferred term	Epoetin alfa (N = 279) n (%)	Placebo (N = 175) n (%)	Total (N = 454) n (%)
Number of Subjects Reporting Adverse Events	235 (84.2)	147 (84.0)	382 (84.1)
myocardial infarction	**4 (1.4)**	**2 (1.1)**	**6 (1.3)**
chest pain	**30 (10.8)**	**18 (10.3)**	**48 (10.6)**
device malfunction	**12 (4.3)**	**4 (2.3)**	**16 (3.5)**
medical device complication	**3 (1.1)**	**0 (0)**	**3 (0.7)**
blood creatinine increased	3 (1.1)	0 (0)	3 (0.7)
blood potassium increased	8 (2.9)	2 (1.1)	10 (2.2)
blood pressure increased	19 (6.8)	11 (6.3)	30 (6.6)
fluid overload	**3 (1.1)**	**0 (0)**	**3 (0.7)**
convulsion	**5 (1.8)**	**3 (1.7)**	**8 (1.8)**
erythema	**7 (2.5)**	**1 (0.6)**	**8 (1.8)**
rash	**10 (3.6)**	**6 (3.4)**	**16 (3.5)**
hypertension	**59 (21.1)**	**20 (11.4)**	**79 (17.4)**
thrombosis	4 (1.4)	1 (0.6)	5 (1.1)
vascular occlusion	12 (4.3)	2 (1.1)	14 (3.1)

Reduced Dialysis Efficiency

The sponsor classified the terms highlighted in yellow as those representative of reduced dialysis efficiency as a result of Epogen treatment. Acidosis (not shown) was also included in this group but did not meet the criteria for being > 1% in the Epogen arm (0.7% vs 0%). Although these combined events are discussed in the label as *reduced dialysis efficiency* in the dialysis management section (5.8) and the proposed table references section 5.8, the rate of device malfunction in the Epogen arm is very nearly twice that of the Placebo arm and is reflective of a plausible biologic basis. **It is**

therefore recommended that the Device Malfunction (4.3%) appear in the Adverse Reaction table.

Medical Device Malfunction was further analyzed in the dialysis-only study groups and found to represent 12/148 (8.1%), 4/96 (4.2%), and 16/244 (6.6%) of Epogen, Placebo, and Total groups, respectively. This rate is nearly twice that in the Placebo population and bears biologic plausibility to the mechanism of action of Epogen. **It is therefore recommended that Medical Device Malfunction (8.1%) be added to the Adverse Reaction table.**

While medical device malfunction and medical device complication are obviously confined to the dialysis population, the terms blood creatinine increased and blood potassium increased are not. Further reviewer analysis of these two terms in the total, pre-dialysis, and dialysis populations was therefore indicated. The following table (Table 3) summarizes the results of this review.

Table 3: Reviewer Analysis of Hyperkalemia and Blood Creatinine Increased

Hyperkalemia + Blood Potassium Increased	EPO	Placebo	Total
All (EPO/e8701, JNJ/86-001, 86-004, 86-011, 87-054)	19/279 (6.8)	9/175 (5.1)	28/454 (6.2)
PreDialysis (JNJ/86-011 and 87-054)	3/131 (2.3)	3/79 (3.8)	6/210 (2.9)
Dialysis (EPO/e8701, JNJ/86-001, 86-004)	16/148 (10.8)	6/96 (6.25)	22/244 (9.0)
Blood Creatinine Increased	**EPO**	**Placebo**	**Total**
All (EPO/e8701, JNJ/86-001, 86-004, 86-011, 87-054)	3/279 (1.1)	0/175 (0)	3/454 (0.7)
PreDialysis (JNJ/86-011 and 87-054)	Not Provided in Pre-Dialysis Table		
Dialysis (EPO/e8701, JNJ/86-001, 86-004)	3/148 (2.0)	0/96 (0)	3/244 (1.2)

The higher combined rates of Hyperkalemia + Blood Potassium Increased were primarily the result of increased rates in the dialysis population, although it is reasonable to include this as a feature of reduced dialysis efficiency, the rate exceeds that in the placebo group by a significant degree. **It is therefore recommended that Hyperkalemia (10.8%) be added to the Adverse Reaction table with a footnote denoting its applicability solely to the Dialysis Population.**

Chest Pain and Myocardial Infarction

Chest pain was deemed to represent a symptom, not a medical diagnosis, and the difference between Epogen and Placebo treated groups was < 1 %. It was therefore not considered an ADR. In addition, Angina Pectoris occurred at a rate less than placeboe (2.9% vs 4.0%).

(b) (4)

The sponsor acknowledges that in the NHCT and CHOIR studies, groups randomized to higher hemoglobin targets experienced higher rates of a combined endpoint that included myocardial infarction. This issue is a

prominent feature of other aspects of the label (Black Box Warning, Warnings and Precautions). Despite this rationale, Myocardial Infarction is an important Event of Special Interest for this drug class. The difference, while less than 1%, still represents an important increase over placebo-treated patients. **It is therefore recommended that Myocardial Infarction (1.4%) be included in the Adverse Reaction table.**

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.

Hypertension, Rash, and Vascular Access Thrombosis

In the sponsor analysis of Hypertension, Rash (includes erythema), and Vascular Access Thrombosis, the following tables were produced:

Table 4: Sponsor Analysis of Rash (by Related Terms) from the Analyzed Studies

COMBINED TERM	Epoetin alfa (N = 279)	Placebo (N = 175)	Total (N = 454)	Studies
preferred term	n (%)	n (%)	n (%)	EPO/e8701
RASH	**19 (6.8)**	**8 (4.6)**	**27 (5.9)**	JNJ/86-001
erythema	7 (2.5)	1 (0.6)	8 (1.8)	86-004
rash	10 (3.6)	6 (3.4)	16 (3.5)	86-011
rash macular	1 (0.4)	0 (0)	1 (0.2)	87-054
rash maculo-papular	1 (0.4)	0 (0)	1 (0.2)	
rash pruritic	1 (0.4)	1 (0.6)	2 (0.4)	

Table 5: Sponsor Analysis of Elevated Blood Pressure (by Related Terms) from the Analyzed Studies

COMBINED TERM	Epoetin alfa (N = 279)	Placebo (N = 175)	Total (N = 454)	Studies
preferred term	n (%)	n (%)	n (%)	EPO/e8701
ELEVATED BLOOD PRESSURE	**77 (27.6)**	**33 (18.9)**	**110 (24.2)**	JNJ/86-001
blood pressure diastolic increased	1 (0.4)	1 (0.6)	2 (0.4)	86-004
blood pressure increased	19 (6.8)	11 (6.3)	30 (6.6)	86-011
blood pressure systolic increased	0 (0)	1 (0.6)	1 (0.2)	87-054
hypertension	59 (21.1)	20 (11.4)	79 (17.4)	

Table 6: Sponsor Analysis of Vascular Access Thrombosis (by Related Terms) from the Analyzed Studies (in Dialysis Patients)

COMBINED TERM	Epoetin alfa (N = 148)	Placebo (N = 96)	Total (N = 244)	Studies
preferred term	n (%)	n (%)	n (%)	EPO/e8701
VASCULAR ACCESS THROMBOSIS	**33 (22.3)**	**21 (21.9)**	**54 (22.1)**	JNJ/86-001
arteriovenous fistula thrombosis	19 (12.8)	19 (19.8)	38 (15.6)	86-004
graft thrombosis	5 (3.4)	4 (4.2)	9 (3.7)	
vascular occlusion	12 (8.1)	2 (2.1)	14 (5.7)	

In terms of the Table 5, the sponsor found that the rates between Epogen treated and Placebo treated patients were similar (<1% difference) and therefore were not included in the ADR table (the term 'vascular occlusion' was used to define vascular access thrombosis in study 86-004).

Final Table Based on Combined (Sponsor and Reviewer) Analysis

The above considerations yielded the following conclusions:

1. The yellow-highlighted terms referring to dialysis management issues, myocardial infarction, chest pain, convulsion, and vascular occlusion were removed from Table 2
2. The terms rash and erythema were combined (by the sponsor) yielding an updated incidence rate based on Table 3
3. Rates for hypertension can be updated based on Table 4

Conclusion

Following review of the submitted material, it is recommended that the Adverse Reaction table for CRF patients be amended as follows:

Table 7: Reviewer Constructed Adverse Reaction Table for CRF Patients

Final **preferred term**	**Epoetin alfa (N = 279) n (%)**	**Placebo (N = 175) n (%)**	**Total (N = 454) n (%)**
Number of Subjects Reporting Adverse Events	235 (84.2)	147 (84.0)	382 (84.1)
hypertension	**59 (21.1)**	**20 (11.4)**	**79 (17.4)**
hyperkalemia**	**16/148 (10.8)**	**6/96 (6.25)**	**22/244 (9.0)**
medical device malfunction**	**12/148 (8.1)**	**4/96 (4.2)**	**16/244 (6.6)**
rash/erythema	**19 (6.8)**	**8 (4.6)**	**27 (5.9)**
thrombosis*	**4 (1.4)**	**1 (0.6)**	**5 (1.1)**
myocardial infarction	**4 (1.4)**	**2 (1.1)**	**6 (1.3)**
fluid overload	**3 (1.1)**	**0 (0)**	**3 (0.7)**

***not including vascular access thrombosis**
****only applicable to dialysis patients**

It is left to the discretion of the sponsor as to how best the above information shall be presented in the PLR. The sponsor may choose to display the dialysis-specific information as shown (with a paragraph describing the dialysis studies and rates of complications), or as a separate table specific to dialysis patients.

Zidovudine Treated Patients with HIV

In the review of adverse events for HIV patients involved in clinical trials, the overall effects of HIV, as well as those potentially manifested by Highly Active Anti-Retroviral Therapy (HAART) must be taken into account. Adjudication of adverse events, therefore, is sometimes complicated by the recognition that some reported events can be confounded by the underlying natural history of the disease or medication regimen.

Demographics

A total of 297 AZT-treated HIV-infected subjects were studied in 4 placebo-controlled studies (EP87-020, EP87-021, H87-037, and I88-009). A total of 144 (48%) subjects were randomly assigned to receive PROCRIT and 153 (52%) were randomly assigned to received placebo. PROCRIT was administered at doses between 100 and 200 IU/kg t.i.w., s.c., for up to 12 weeks. For the combined PROCRIT-treatment groups, a total of 135 men and 3 women between the ages of 24 and 64 years were enrolled. The racial

distribution of the combined PROCRIT-treatment groups was as follows: 129 white, 15 other.

Methodology

In reviewing adverse event terms in HIV patients from the above stated trials, the sponsor adhered to the following protocol:

1. All adverse event terms with an incidence of 1% or greater were evaluated separately by indication system according to the assessment algorithm defined by the Johnson & Johnson Pharmaceutical Research & Development, LLC (J&JPRD) Benefit Risk Management (BRM) group.

2. The ADRs were reviewed for consistency across all indications to identify common ADRs and by indication to identify any ADRs that might be unique to a specific population.

3. Dose response effects were evaluated when available.

4. Adverse events with an incidence of 1% or greater were assessed in a relevant Phase 4 study (SPINE for surgery), for consistency with events from the primary studies.

5. Biological plausibility was assessed by a committee of at least 3 to 4 J&JPRD clinicians (including the BRM specialist) and consensus was reached regarding assignment of ADR status.

Presented below by indication are adverse event terms included in the USPI that have been deleted, as they did not meet the criteria for inclusion as an ADR in the Clinical Trial section, or have been recoded to a corresponding MedDRA term, or have been included in the Postmarketing Experience section of the USPI. "Death" is an outcome rather than an ADR and has been addressed in the **Boxed Warnings** and **Warnings** sections of the USPI.

Terms Deleted From the Zidovudine-treated HIV-infected Patients
Indication (with rationale for exclusion; percentages are for Procrit vs. Placebo, respectively)

- **Pyrexia**
  - 42% vs 34%; Epo ≤ 2x PBO; confounded by study population
- **Fatigue**
  - 26% vs 28%; a symptom of both infectious illness and anemia
- **Headache**
  - 19% vs 21%; a common complaint, often accompanying pyrexia, which in turn is a common symptom of infection; not biologically plausible
- **Cough**
  - 26% vs 14%; EPO ≤ 2x PBO; not biologically plausible, possibly related to comorbid conditions.
- **Diarrhea**
  - 30% vs 33%; lacks biologically plausible mechanism, confounded by underlying disease

- **Congestion, Respiratory**
  - pulmonary congestion and nasal congestion were 3% vs 1% and 13% vs 5% but lacks biologic plausibility and may be confounded by comorbid conditions
- **Nausea**
  - 25% for both EPO and PBO; lacks biologic plausibility
- **Shortness of Breath**
  - 1% for both EPO and PBO groups; dyspnea exertional 4% vs 7%, dyspnea 17% vs 17%; lacks biologic plausibility and confounded by potential concurrent illness
- **Asthenia**
  - 23% vs 21%; a common complaint associated with anemia and in patients with viral infections; an imprecise term.
- **Skin Reaction, Medication Site**
  - In MedDRA, the term "medication site" corresponds to "injection site." Injection site terms occurred at very low incidence in clinical studies, and many injection-site related terms (including hemorrhage) were higher in the placebo treatment group. J&JPRD proposes the addition of "injection site reaction, including pain and irritation" to the Postmarketing Experience Section of the USPI as an ADR.
- **Dizziness**
  - 30% vs 33%; not biologically plausible, confounded by underlying disease state.

The following terms were reviewed by the sponsor by grouping of related terms. The incidence rates between Procrit and Placebo treated subjects were then compared. The terms are followed by rationale for their inclusion or exclusion from the final table.

(b) (4)

The Table contained in Attachment 3 (HIV: Incidence of Adverse Reactions by Body System and Preferred Term) was reviewed line-by-line and the adjudication of terms evaluated. This reviewer found the sponsor adjudication of terms to be rational and reasonable and is in agreement with the deletion of selected terms from further analysis.

The sponsor proposes the following Adverse Reaction table for the HIV patients section.

Table 8: Proposed Adverse Reaction Table for Zidovudine Treated Patients with HIV Infection

(b) (4)

[redacted]

Conclusion

The submitted table appears acceptable.

Surgery Patients

Demographics

Four hundred sixty-one subjects undergoing major orthopedic surgery were studied in a comparative dosing study (Study N93-057; 2 dosing regimens) and 1 placebo-controlled study (Study M92-011) A total of 358 (78%) subjects were randomly assigned to receive PROCRIT and 103 (22%) were randomly assigned to received placebo. PROCRIT was administered daily at a dose of 100 to 300 IU/kg s.c. for 15 days, or at 600 IU/kg once weekly for 4 weeks. For the combined PROCRIT-treatment groups, a total of 90 men and 268 women between the ages of 29 and 89 years were enrolled. The racial distribution of the combined PROCRIT-treatment groups was as follows: 192 white, 64 black, 7 other.

One open-label study (SPINE in surgery) was also examined for ADRs not identified in the blinded studies listed above. Study N93-057 was a randomized, open-label, dose ranging study and was included in the evaluation of ADRs for the surgical indication. ADRs were selected based on possible relationship to PROCRIT and clinical relevance.

Methodology

The following data were reviewed: 1) Adverse events that occurred at an incidence of 1% or greater in at least 1 study; 2) Adverse events that occurred at any frequency that did not appear in the double-blind controlled studies; and 3) serious adverse events that did not appear in the double-blind controlled studies.

Presented below by indication are adverse event terms included in the USPI that have been deleted, as they did not meet the criteria for inclusion as an ADR in the Clinical Trial section, or have been recoded to a corresponding MedDRA term, or have been included in the Postmarketing Experience section of the USPI. "Death" is an outcome rather than an ADR and has been addressed in the **Boxed Warnings** and **Warnings** sections of the USPI.

Terms Deleted From the Surgery Indication

- **Pyrexia**
  - 15-29% vs 26%; when information was combined for all Procrit treatment groups the incidence was lower 17% vs 26%
- **Nausea**
  - 43-56% vs 45%; 45% in combined Procrit study groups vs 45% in placebo; incidence potentially confounded by comorbid conditions
- **Constipation**
  - 42-54% vs 43%; 42% in combined Procrit groups vs 43% in placebo; confounding likely
- **Skin Reaction, Medication Site**
  - The MedDRA term most likely corresponding to "medication site" was injection site reactions. No clear pattern of injection site adverse event incidence was observed with some events having higher incidence in the PROCRIT-treatment group, others in the placebo-treatment group. J&JPRD proposes the addition of "injection site reaction, including pain and irritation" to the Postmarketing Experience Section of the USPI as an ADR.
- **Vomiting**
  - 12-28% vs 14% with no clear dose-effect relationship; confounding likely, lacks biological plausibility
- **Skin Pain**
  - Skin pain is not a MedDRA term and the rationale for not including this term as an ADR is presented above under the term skin reaction (medication site). J&JPRD proposes the addition of "injection site reaction, including pain and irritation" to the Postmarketing Experience Section of the USPI as an ADR.
- **Pruritus**
  - 12-21% vs 14%; combined incidence 16% vs 14%; no clear dose relationship
- **Insomnia**
  - 13-21% vs 13%; combined incidence 15% vs 13%; lack of biologically plausible mechanism
- **Headache**
  - 10-18% vs 12%; combined incidence 12% vs 12%
- **Dizziness**
  - 7-15% vs 12%; combined incidence is 8% vs 12%; lack of biologically plausible basis
- **Urinary Tract Infection**
  - 3-11% vs 10%; combined incidence 7% vs 10%; confounding likely due to presence of foley catheter and postoperative setting. Causal relationship not biologically plausible.
- **Hypertension**
  - 5-11%; 9% for the placebo group; for combined Procrit-treatment groups from the placebo-controlled study, the incidence was 4%; no clear dose-effect was observed.
- **Diarrhea**
  - 6-10% vs 12%; combined incidence 8% vs 12%; causal relationship not biologically plausible.
- **Dyspepsia**
  - 7-12% vs 9%; 11% vs 9% in the placebo controlled study vs placebo. However, a causal relationship lacks biologic plausibility
- **Anxiety**
  - 2-10% vs 11%; combined incidence 5% vs 11%; causal relationship not biologically plausible

(b) (4)

(b) (4)

The sponsor proposes the following Adverse Reaction table for the PLR.

Table 9: Sponsor's Proposed Adverse Reaction Table for Surgery Patients

(b) (4)

Conclusion

The proposed adverse reaction table is acceptable.

4. Labeling Review: Submitted PLR for Epoetin alfa (Epogen)

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 (10/9/08). 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 (for example, sponsor submitted *Section 5.4 Lack or Loss of Response*, containing a differential diagnosis for anemia, was removed).
- 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 (for example, vCJD risks associated with albumin containing products)

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 *anemia associated with* was changed to [redacted] (b) (4) to improve clarity regarding the source of anemia for which Epogen is indicated.

Dosage and Administration

Reviewer's Comment(s):

- For the Surgery Patients indication a *total* duration of therapy (14 days) was preferred over the specific prescription for therapy (10 days prior to surgery, day of surgery, and 4 days after surgery). The reader is referred to the specific Dosage and Administration section (2.2) for the details of dosing.

Contraindications

Reviewer's Comment(s):

- "Known hypersensitivity to mammalian cell-derived products or Albumin (Human)" was removed. PLR Labeling Review Tool (LRT) advises avoidance of the inclusion of theoretical contraindications.

Warnings and Precautions

Reviewer's Comment(s):

- Reference to the greater risk of cardiovascular morbidity and mortality in hyporesponsive patients was added to the label in response issues raised in the Normal Hematocrit Study and other studies reviewed at the CRDAC/DsARM Meeting on September 11, 2007.
- Dialysis Management issues were added to the Warnings and Precautions section as these were felt to be relevant to prescribers.
- Language was changed to active voice.

Adverse Reactions
Reviewer's Comment(s):

- Adverse reactions occurring in ≥ 10% of Epogen-treated patients in clinical studies for the various indications were noted. Adverse events occurring less often than placebo were removed from this list. These revisions are felt to reflect clinically relevant frequencies of adverse reactions associated with Epogen use.
- Adverse reactions related to [redacted] (b) (4) was removed; there have not been reports of adverse reactions related to [redacted] (b) (4)

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

- A section on pediatric use was added (*safety & effectiveness in patients ≤ 1 month old have not been established*).

Full Prescribing Information

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

- Subsections were shortened to improve readability.
- Dosing information was removed from certain subsections (ie 1.2) and placed under the Dosage and Administration section.
- It was the impression of both review divisions that the subsections were more effective whent they stated the indications clearly. Including contraindication statements in these sections created confusion about the proper use of Epogen. Contraindications were therefore removed from individual subsections and consolidated into a newly created section: *Section 1.5.1 Epogen is Not Indicated.* The following statements were removed from their respective subsections and consolidated into *Section 1.5.1.*:
    - Section 1.1:
        - *Epogen is not intended for patients who require immediate correction of severe anemia*
    - Section 1.3:
        - *Epogen is not indicated for the treatment of anemia in cancer patients due to other factors such as iron or folate deficiencies, hemolysis, or gastrointestinal bleeding, whcih should be managed appropriately.*

    - *Epogen has not been demonstrated in controlled clinical trials to improve the symptoms of anemia, quality of life, fatigue, or patient well-being.*
    - *Epogen is not indicated for use in patients receiving hormonal agents, therapeutic biologic products, or radiotherapy unless receiving concomitant myelosuppressive therapy.*
  - Section 1.4:
    - *Epogen is not indicated for anemic patients who are willing to donate autologous blood.*

Dosage and Administration (2)

Reviewer's Comment(s):

- (b) (4) 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 submitted PLR document contained a table which contained both starting dose and dose adjustment information. This was separated into two sections – *Starting Dose* and *Dose Adjustment*. A tabular format was opted for in order to maintain clarity.
- Venous-line administration (dialysis patients) and home administration information was removed. These issues are addressed in the Patient Information document.
- The *Maintenance Dose* section was consolidated into the *Dose Adjustment* section was revised for clarity. (The instruction *Evaluate and treat for other causes of anemia* was removed as it was felt to represent a common-sense clinical practice issue).
- In Cancer Patients and Zidovudine treated patients, the assessment of circulating erythropoietin levels was removed. For Zidovudine treated patients, this information was moved to the *Indications and Usage* section. Sections entitled *Starting Dose* and *Dose Adjustment* now contain essential dosing information (in bulleted format) as well as instructions to stop Epogen if the patient does not respond after 8 weeks.
- Amgen is asked to comment on current clinical practice regarding TIW dosing of Epogen in Cancer Patients.
- In *Surgery Patients*, dosing instructions were changed to a bulleted format to enhance readability.
- In *Preparation and Storage*, aseptic technique was removed because it is considered a standard-of-care measure. Detailed information regarding administration is addressed in detail in the *Patient Information* section.

Dosage Forms and Strengths (3)

Reviewer's Comment(s):

- This section was shortened for clarity; information regarding excipients and vial/syringe formulation is described in detail in section 16 *How Supplied/Storage and Handling.*

Contraindications (4)
Reviewer's Comment(s):

- This section was expanded to more clearly state populations in whom Epogen should not be used.

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 (5.6), Albumin (Human) (5.7).*
- Rather than reiterating dose adjustment material in section 5.3, readers are instead referred to *Dosage and Administration* for dose management issues. Amgen is asked to provide data on hypertensive encephalopathy for this section, if it exists.
- *5.8 Hematology* section was replaced with *Laboratory Monitoring.* Information contained within *Hematology* is already contained elsewhere (*Pharmacodynamics* and *Laboratory Monitoring*). In addition, *exacerbation of porphyria* was moved to section *6.2 Postmarketing Experience*.
- (b) (4) was consolidated into *Laboratory Monitoring* and *5.9 Pedatrics: Risks in Premature Infants* was moved to *Contraindications.* These changes were felt to improve the relevance of information contained within the respective subsections.

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):

- *Serious Allergic Reactions* was added to this section.
- **It is noted that the following required statement was inadvertently omitted from the proposed draft statement (Section 6.1 Clinical Trial Experience) sent to Amgen and should be reinserted.**
    - Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of Epogen cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice.
- The proposed Clinical trial paragraph under *Chronic Renal Failure Patients* was reviewed within the Division and the following conclusions were drawn.
    - In the Sponsor's review of completed, placebo-controlled trials, the rationale outlined for determining which Adverse Events qualified as Adverse Reactions were in keeping with the Guidance for Industry document cited above.
    - See the review above concerning the addition of Fluid Overload in the Adverse Reaction table for CRF patients.

- The Table: Incidence of Adverse Events by Preferred Term (EPO STUDIES: EP87-020, EP87-021, H87-037, I88-009) and Appendix 2.2: **Adverse Events** With an Incidence of 1% or Greater From HIV Studies Using PROCRIT (Terms Combined For Hypertension, Rash, And Thromboembolic Events) were reviewed; the submitted table for Zidovudine Treated HIV Infected Patients appears acceptable.
- Appendix 1.4: Adverse Events With an Incidence of 1% or Greater From Placebo-Controlled Surgery Studies Using PROCRIT, and Appendix 2.3: Adverse Events With an Incidence of 1% or Greater From Surgery Studies Using PROCRIT (Terms Combined For Hypertension, Rash, And Thromboembolic Events) were reviewed. The submitted table for Surgery Patients appears acceptable.

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

- (b) (4) Porphyria was added to the bulleted list of Postmarketing Experience items.

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 Patients on Dialysis, Pediatric Patients Not Requiring Dialysis, Pediatric HIV-Infected Patients, Geriatric Use sections.

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 (10) and Pharmacology (12)

Reviewer's Comment(s):

- Aspects of these sections (which are somewhat related) were combined under *Description* in order to shorten the *Mechanism of Action* statement to one sentence.
- The information under the proposed *Zidovudine-treated HIV-infected Patients* section was reduced in consideration that the same information was presented in Section 1.2 and in the Clinical Trials section related to HIV patients.

Nonclinical Toxicology (13)

Carcinogenesis, Mutagenesis, Impairment of Fertility (13.1) and Reproductive and Developmental Toxicology (13.3)

Reviewer's Comment(s):

- Information pertaining to preclinical studies brought from Pregnancy (8) to Section 13.3 in order to maintain species-specific information in the appropriate section.

Clinical Studies (14)

Chronic Renal Failure Patients (14.1)

Reviewer's Comment(s):

- The table displaying starting dose and expected hemoglobin increase was removed because it was not felt to add significantly to what was already contained within Dosage and Administration
- The summary paragraph related to the 26 week, double-blind, placebo-controlled study of 118 patients with an average Hemoglobin of 7 g/dL experiencing increases in hemoglobin and exercise tolerance was moved to the Adult Patients on Dialysis section.
- The section therefore starts at Adult Patients on Dialysis. Information regarding *individualization of dosing* and the percentage of patients in clinical trials requiring various dose ranges was removed from this section as it was not felt to be sufficiently important and because many aspects were already contained within the dosage and administration section.
- No major changes were made to the Pediatric Patients on Dialysis or Patients with CRF Not Requiring Dialysis Sections.

Zidovudine-Treated Patients with HIV Infection (14.2), Surgery Patients (14.4)

Reviewer's Comment(s):

- Information related to opportunistic infections, p24 antigen levels, and responsiveness of Zidovudine-treated HIV patients was removed.
- 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):

- The information from Section 3 Dosage Forms and Strengths and Section 16 How Supplied/Storage and Handling were switched.
- The Patient Counseling Section was reorganized into a bulleted presentation and information specific to home use refers patients to the Patient Instructions for Use
- Section 17.2 is intended to eventually contain the Medication Guide.

5. Conclusions

Overall, the submitted revisions appear acceptable. In review of the submitted data, it was determined that Fluid Overload should be added to the CRF Adverse Reaction table (or justification provided as to why it shouldn't).

6. Recommended Regulatory Action

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

MEMORANDUM

To: **Monica Hughes, M.S.**
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: **October 14, 2008**

Re: **Comments on draft labeling for Epogen (epoetin alfa)**
STN 103234/5166

We have reviewed the proposed label for Epogen (FDA version dated 10/9/08) 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.

19 Page(s) of Draft Labeling has been Withheld in Full immediately following this page as B4 (CCI/TS)

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

Memorandum

Date: October 9, 2008

From: Monica Hughes, M.S., Lead, Regulatory Health Project Manager
DBOP/OODP/OND/CDER/FDA

Subject: STN BL 103234/5166: FDA Proposed Revisions to the Epogen PLR Label

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Please find attached FDA's counter-proposed labeling revisions to the Epogen label contained in your April 23, 2008, submission to STN BL 103234/5166. Attached is a clean copy of our initial proposed changes along with a compare-merge Word document showing the FDA proposed redlined changes against your April 23, 2008, label. FDA requests that Amgen incorporate parallel labeling changes in the Procrit labeling consistent with the Epogen labeling and it include it with your response.

Please note that additional FDA comments may follow upon receipt of your response. FDA may have additional comments regarding the PLR format from our SEALD colleagues, as well as additional comments from our DDMAC colleagues.

Please find attached below, FDA's rationale for our proposed labeling revisions.

FDA requests that Amgen does not finalize or print this labeling until FDA, Amgen, and J&J PRD reach agreement on final language regarding the draft labeling.

FDA requests that Amgen and J&J PRD respond to this communication with revised, redlined labeling, by October 15, 2008.

FDA's rationale for changes to the following labeling sections:

1. **Boxed Warning**
   a. "minimize" changed to "decrease" because of the lack of certainty regarding the magnitude of the reduction in the risk in patients who receive any amount of an ESA.
   b. [redacted] (b) (4)
   c. "adverse reactions" substituted for "events" throughout labeling.

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

3. **Dosage and Administration**
   a. New [redacted] (b) (4) subsection created to limit repetition of the same information across multiple indications.
   b. Directions for patient monitoring deleted from this section to limit repetition; where necessary, such information is described under Warnings and Precautions (e.g., Hypertension, Laboratory Monitoring).
   c. Elimination of redundant text (e.g., both text and table provide essentially the same dosing directions for patients with chronic renal failure).
   d. Elimination of rationale for dosing directions (e.g., "response time of the hemoglobin to a dose increase can be 2 to 6 weeks") or preparation and administration (e.g., prolonged vigorous shaking may denature…").
   e. References to [redacted] (b) (4) deleted; these data are cited in context in the Clinical Studies section.
   f. References to "lack or loss of response" deleted; product labeling is not intended to cover aspects of general medical management (e.g., differential diagnosis of anemia) and clinical indications clarify the types of anemia for which Epogen is indicated.
   g. "maintenance dose" subsections deleted; information in these subsections generally overlap with information in the "dose adjustment" subsections, which were retained and re-worded for brevity and active voice.

4. **Dosage Forms and Strengths**
   a. Information in this section moved to section 16; remaining information shortened for brevity and consistency with other labeling.
   b. References to the [redacted] (b) (4) deleted; [redacted] (b) (4)

5. **Contraindications**
   a. Replaced contraindication regarding theoretical allergic reactions to subcomponents with more specificity to serious allergic reactions as report in post-marketing experience and in Warnings/Precautions.
   b. Added contraindication regarding benzyl alcohol containing formulations in given the availability of an alternative formulation and consistent with proposed wordings in

other sections not to use the benzyl alcohol containing formulation in pregnant women, neonates and infants due to documented risks with other products.

6. **Warnings and Precautions**

a. (b) (4)

b.

c. Section 5.2: Editorial changes to remove the word "Cancer" from the study titles as this may lead to confusion with references to studies in section 14.3. Also, references to the study phase (e.g., phase 3) deleted throughout this section, as superfluous to other information describing study design and as per FDA Guidance. Deleted alternate names of studies (e.g., ENHANCE) throughout sections 5.1 and 5.2, as per FDA Guidance on describing clinical studies.

d. (b) (4)

e.

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

g. (b) (4)

h. (b) (4)

i. Section 5.3 (Hypertension) revised to limit redundant dosing information that can be addressed with cross-reference to D&A section. Also deleted unnecessary information (b) (4)

j. Moved up "Seizures" to section 5.4 as next most common serious adverse event. Deleted statement "while the relationship between seizures and rate of rise…." as unnecessary explanation; dosing recommendations already adequately covered in D&A section of labeling.

k. Deleted section on "loss of response". Product labeling should not including information related to general practice of medicine (i.e., differential diagnosis and diagnostic work-up of anemia).

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

m. Deleted subsection on Hematology. First paragraph redundant and covered in subsection on laboratory monitoring and D&A. Second paragraph does not rise to level of "warnings" and has been edited for brevity and moved to the Adverse

Reactions section of the label. The third paragraph is general medical information, unrelated to the product and therefore deleted from product labeling. The fourth paragraph was deleted as it relates to unapproved uses.

n. Subsection on risk in infants deleted- superseded by new Contraindications statement
o. Subsection on Dialysis Management edited for brevity and critical information; theories on potential effects and absence of effects in clinical studies deleted as unnecessary information.
p. Subsection on [redacted] (b) (4) re-titled to clarify the focus of this subsection. Edited for brevity and active voice and to limit redundancy with D&A section.

7. Adverse Reactions

a. Analyses based on pooled datasets appear to underestimate effects observed in individual studies, thus these data have been deleted. Tables for individual studies should delete any rows in which events were more frequent in the control arm than placebo and remaining adverse reactions should be listing in decreasing incidence, based on rates in the Epogen arm.
b. FDA cannot verify data in this table because SAS datasets not supplied (only program files). Please supply SAS transport files and a tabular summary of all adverse events.
c. Hypertension subsection for patients with CRF deleted-to limit redundancy this information is now contained in the Warnings/Precautions subsection on hypertension.
d. In the subsection on adverse events in cancer patients, data from the three-times-per week regimen across six studies was excluded because the small size and heterogeneity which may obscure safety signals and limit truly random allocation as well as the lower drug exposure when compared to the weekly dosing schedule.
e. In the subsection on adverse events in patients scheduled for surgery, data on the SPINE study deleted to limit redundancy- these data are described in the new section 5.1
f. Post-marketing section: Revised to include [redacted] (b) (4) porphyria; this replaces section in precautions that contains no data on incidence and thus appears to be post-marketing reports. Revised section on allergic reactions for brevity and cross-reference more detailed information in the Warnings and Precautions subsection.
g. Immunogenicity subsection: This section contains no data- please see FDA comments regarding provision of data or revision to state that data are not available from clinical studies.

8. Drug Interactions

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

9. Use in Specific Populations

a. Pregnancy Category C: Editorial changes. Added reference to Contraindications and information on risks of benzyl alcohol in premature infants.
b. Nursing mothers: Animal data in this section moved to Non-clinical toxicology section. This section modified in accordance with recommendations from Maternal-Fetal Health team. Reference to Contraindications section added.
c. Pediatric Use: Addition of reference to the Contraindications section and statement that benzyl-alcohol containing formulations should not be used in infants/neonates. Information on study in children with cancer deleted as this study is described in the Clinical Studies section (14). Re-worded for clarity.

d. Geriatric Use: see FDA embedded comment regarding revision to reflect 5 clinical studies. Additional changes for clarity.

10. Overdosage

a. This section was revised to clarify both subacute and chronic effects of overdosage and to provide more specific directions regarding appropriate actions to be taken.

11. Description

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

12. Clinical Pharmacology

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

13. Non-Clinical Toxicology

a. Section on Reproductive and Developmental Toxicology added and includes data previously described under Pregnancy subsection; the non-clinical data were moved to this section as recommended by the OSE consultant staff as the more appropriate section for these data.

14. Clinical Studies

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

15. How Supplied and Handling Information

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

16. Patient Counseling Information

a. Re-worded for 'active voice" and brevity.

48 Page(s) of Draft Labeling has been Withheld in Full immediately following this page as B4 (CCI/TS)

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

Memorandum

Date: March 5, 2008

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

Subject: Initial RPM PLR Review: sBLA 103234/5166 (Epogen/Procrit PI)

Upon review of the Epogen 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, the Procrit label was not submitted by Amgen. I have requested that the Procrit labeling be submitted, but at this time, the comments below reflect the review of the Epogen label and comments should be applied to the Procrit label.

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. "Epogen (epoetin alfa)" appears under the highlights limitation statement, however, "INTRAVENOUS INFUSION" 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 "WARNINGS: INCREASED MORTALITY, SERIOUS CARDIOVASCULAR and THROMBOEMBOLIC EVENTS, and TUMOR PROGRESSION." 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:_____" date 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 "Issued Date: *month* 2007" from the end of the label.

7. Please further revise the highlights section to ensure it meets the ½ page requirement.

With Respect to the FULL PRESCRIBING INFORMATION:

8. 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

9. The black box warning reads "WARNINGS: INCREASED MORTALITY, SERIOUS CARDIOVASCULAR and THROMBOEMBOLIC EVENTS, and TUMOR PROGRESSION." Please revise.

DOSAGE AND ADMINISTRATION:

10. 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 "Intavenous Infusion" instead of "IV" to avoid a greater potential for medication errors should the abbreviation be misread.

11. Immediately following the heading, Amgen has inserted the following text: "IMPORTANT: See BOXED WARNINGS and WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic events." Please delete this sentence.

12. 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. (b) (4) "

CONTRAINDICATIONS:

13. 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:

14. With respect to section 5.10, Albumin (Human), please revise to include the following verbatim statement: "This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin." *(See Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products.)*

ADVERSE REACTIONS:

15. [redacted] (b) (4) This is ultimately a review issue and will be discussed further during labeling negotations.

16. 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 [redacted] (b) (4) with the incidence of antibodies to other products may be misleading."

OTHER COMMENTS:

17. Please note that the revision date at the end of the highlights section replaces the "revision" or "issue" date at the end of the PI or attached PPI. Please delete the "Issue Date" from the end of the PPI.

18. The manufacturing information should not be located at the end of the PI. The patient package insert should immediately follow the package insert and the manufacturing information should be at the end of the patient package insert, at the end of the labeling.