CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
103234Orig1s5166

PHARMACOLOGY REVIEW(S)
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number: BL STN 103234/5166 ; 103234\5166\5010
Supporting document/s: Electronic submission; PLR label
Applicant’s letter date: 10/23/2009
Product: Epoetin alfa (Epogen/Procrit)
Indication: Epogen is indicated for treatment of anemia and reduction of allogeneic RBC transfusions in patients undergoing elective, noncardiac, nonvascular surgery
Applicant: Amgen, Inc.
Amendment type: Physician Labeling Rule (PLR) Supplement
Sequence # 02563
eCTD sequence number 0199
CDER receipt date 10/26/2009
Review Division: Division of Hematology Products (DHP), Office of Oncology Drug Products (OODP), Office of New Drugs (OND), CDER
Reviewer: Yanli Ouyang, MD, PhD, DABT
Supervisor: Haleh Saber, Ph.D.
Division Director: Ann Farrell, MD
Project Manager: Ebla Ali Ibrahim, MS

Yanli Ouyang 3/25/10
Halle Saber 3/25/2010
1 Executive Summary

1.1 Recommendation on Approvability

From a nonclinical perspective, approval is recommended.

1.1.3 Labeling

No new nonclinical data were submitted or reviewed. All nonclinical recommendations for changes to the Epoetin alfa label were made in compliance with the content and format requirements of labeling for human prescription drug and biological products (21 CFR 201.56(d) and 201.57; the "Physician's Labeling Rule"). Dr. Andrew McDougal in the Division of Biologic Oncology Products has reviewed the related information and recommended the changes for the label. The review team including this reviewer has discussed and revised the changes and concurred with the final recommended changes. Dr. Andrew McDougal will document the rationales for changes made to the nonclinical sections of the label in his review.
MEMORANDUM

TO: The file
CC: Patricia Keegan, M.D., Director, Division of Biologic Oncology Products,
Office of Oncology Drug Products, CDER
FROM: Anne M. Pilaro, Ph.D, Supervisory Toxicologist, Pharmacology/Toxicology-
Branch, Division of Biologic Oncology Products, OODP, CDER

STN BLA #: 103234/5166/5010
SPONSOR: Amgen, Inc.
PRODUCT: epoietin alfa (Epogen®, Procrit®; erythrocyte stimulating factor)
SUBMISSION TYPE: supplemental BLA application; post-approval supplement;
Physician's Labeling Rule (PLR) conversion
DATE: March 24, 2010

SYNOPSIS:
Amgen has submitted a post-approval, supplemental BLA application to affect changes
to the labeling for epoietin alfa (Epogen®, Procrit®), to be compliant with the content and
format requirements of labeling for human prescription drug and biological products (21
CFR 201.56(d) and 201.57; the "Physician’s Labeling Rule"). The nonclinical sections
of the new labeling that were affected were the Indications and Usage statement in the
Highlights of Prescribing Information section, Section 8.1 (Use in Specific Populations:
Pregnancy), and Nonclinical Toxicology Sections 13.1 (Carcinogenesis, Mutagenesis,
Impairment of Fertility), 13.2 (Animal Toxicology and/or Pharmacology) and 13.3
(Reproductive and Developmental Toxicology).

There was no new nonclinical information submitted with the present supplemental
application. Changes made to the labeling are summarized by the primary reviewer,
Andrew J. McDougall, Ph.D. in his review, and did not substantially change either the
scope or the interpretation of the information conveyed. I concur with the proposed
changes in the labeling and with Dr. McDougall’s rationale for the revised language, and
have no further changes to request. Final labeling has been conveyed to the sponsor.

A copy of Dr. McDougall’s review, with supervisory sign-off, has been conveyed to the
regulatory project manager for inclusion in the final action package. No additional
action is indicated from the nonclinical discipline.
Application number: BL STN 103234/5166 ; 103234/5166/5010
Supporting document/s: Accessed electronically via:
\cbiap58\im\eCTD_Submissions\STN103951\103951.enx
Applicant’s letter date: 10/23/2009
Product: Epoetin alfa (Epogen/Procrit)
Indication: Epo gen is an erythropoiesis-stimulating agent (ESA) indicated for:
  o Treatment of anemia due to
    o Chronic renal failure (CRF), in patients on dialysis and not on dialysis
    o Zidovudine in HIV-infected patients
    o The effects of concomitant myelosuppressive chemotherapy that will be administered for a minimum of two additional months in patients with non-myeloid malignancies
  o Reduction of allogeneic RBC transfusions in patients undergoing elective, noncardiac, nonvascular surgery
Applicant: Amgen, Inc.
Amendment type: Physician Labeling Rule (PLR) Supplement
Sequence # 02563
eCTD sequence number 0199
CDER receipt date 10/26/2009
Review Division: Division of Biologic Oncology Products (DBOP), Office of Oncology Drug Products (OODP), Office of New Drugs (OND), CDER
Reviewer: Andrew J. McDougal, Ph.D., D.A.B.T. HFD-107
Supervisor/Team Leader: Anne M. Pilaro, Ph.D. HFD-107
Division Director: Patricia Keegan, M.D.
Project Manager: Mona Patel, Phrm.D.
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1 Executive Summary

1.1 Recommendation on Approvability

From a nonclinical perspective, approval is recommended.

1.2 Previous Communications to the Sponsor and Response:

- On 10/24/2008, a complete response (CR) letter was sent for STN BL 103234/5166 (Keegan/Storm); it noted:
  "We have completed the review of your supplement, and have determined that we cannot approve this supplement in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues. ..."

NONCLINICAL
2. Given the multiple dosing schedules listed in the labeling and the varied testing schedules employed, we are unable to determine the source of the data used to derive the multiples of human exposure from the rat and rabbit reproductive toxicology studies (contained in Section 8.2 of the label). Please identify the source of these data by study number, and whether they were submitted to the original BLA application, or to subsequent supplement application(s). Please also provide copies of the final study reports for each study from which these data were obtained."

- On 10/23/2009 (EDR #0199), the sponsor provided the following nonclinical study reports (as text-searchable pdf files):
  - "Fertility study of KRN5702 by intravenous administration in rats" (267 pages). Study # NRILS 86-1725
  - "Teratology study of KRN5702 by intravenous administration in rats" (311 pages). Study # NRILS 86-1726.
  - "Teragenicity study of KRN5702 by intravenous administration in rabbits" (124 pages). Study # NRILS 87-2216.
  - "Perinatal and postnatal study of KRN5702 by intravenous administration in rats" (295 pages). Study # NRILS 87-2316.

This reviewer verified that KRN5702 is epoetin alfa.

Submission of these four study reports resolves the nonclinical issue identified in the 10/24/2008 CR letter. These 4 study reports were considered for the PLR conversion, but were not fully re-reviewed. The sponsor proposed revised language (please see below).
1.3 Labeling

No new nonclinical data were submitted or reviewed. All nonclinical recommendations for changes to the Epoetin alfa label were made in compliance with the content and format requirements of labeling for human prescription drug and biological products (21 CFR 201.56(d) and 201.57; the “Physician’s Labeling Rule”).

The pivotal nonclinical issue for this PLR was how to best present the nonclinical doses tested in the developmental and reproductive toxicity (DART) tests, for clarity and ease of understanding by physicians and other readers. The calculations used to determine relative exposure to Epoeitin alfa in the nonclinical DART studies versus the recommended patient dose were revised to reflect label updates to the patient dosage information.

Based on recommendations from this reviewer, the review team revised the label to describe the nonclinical doses using the same units as patient dosing (i.e. units/kg), and related the nonclinical doses to the range of patient starting doses (see below). No attempt to extrapolate based on PK was made since the DART studies did not include PK monitoring, and because of the variability observed in the human PK results. Specifically, in section 12.3 Pharmacokinetics of the revised label, data are provided regarding the magnitude of differences in PK across different indications and in patients compared to healthy volunteers; the current label also notes the limitations of the human PK knowledge base.

In previous versions of the label, the nonclinical doses were benchmarked to a single patient dose level. In the current label, Section 2 Dosage and Administration provides information regarding multiple starting doses; the ability to benchmark to a single dose level is further complicated by PLR label directions to adjust dosing based on patient response. This table was extracted from the proposed PLR label information:

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Recommended start doses</th>
<th>Dosing adjustment recommendations?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic renal failure patients – adults</td>
<td>50 to 100 units/kg 3x weekly</td>
<td>Yes</td>
</tr>
<tr>
<td>Chronic renal failure patients – pediatric</td>
<td>50 units/kg 3x weekly</td>
<td>Yes</td>
</tr>
<tr>
<td>Zidovudine-treated HIV-infected patients</td>
<td>100 units/kg 3x weekly</td>
<td>Yes</td>
</tr>
<tr>
<td>Cancer patients on chemotherapy – adults</td>
<td>150 units/kg 3x weekly</td>
<td>Yes</td>
</tr>
<tr>
<td>Cancer patients on chemotherapy – adults</td>
<td>40,000 units weekly</td>
<td>Yes</td>
</tr>
<tr>
<td>Surgery patients</td>
<td>600 units/kg weekly</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>o 300 units/kg daily for 14 days</td>
<td>No</td>
</tr>
</tbody>
</table>
1.3.1 Nonclinical recommendations for label changes

The following nonclinical changes were made to the Epoetin alfa label during conversion of the label to the PLR format:

1. Under Use in Specific Populations added “Pregnancy: Based on animal data, may cause fetal harm. Pregnancy Surveillance Program is available (8.1).”

2. Under Section 8 Use in Specific Populations, subsection 8.1 Pregnancy:
   a. Added the word “healthy” to describe the nonclinical models.
   b. The sentence “In animal reproductive and developmental toxicity studies, adverse fetal effects occurred when pregnant rats received epoetin alfa at doses approximating the clinical recommended start doses” was moved from the third paragraph to the first paragraph, so that the first paragraph would be a section summary consistent with the PLR label format.
   c. This sentence was added: “This animal dose level of 100 Units/kg per day the clinical recommended start dose, depending on the treatment indication, .”

3. Under Section 13 Nonclinical Toxicology, subsection 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility:
   a. Reformatted the section to include 3 paragraphs (i.e. one for each category listed in the title).
   b. Revised the mutagenicity sentence to begin with a summary phrase, “EpoGen was not mutagenic or clastogenic under the conditions tested: ...
   c. Discussion of the nonclinical fertility study (study # NRILS 86-1725) was moved from section 13.3 to Section 13.1, under Impairment of Fertility.
   d. Under the Impairment of Fertility section, added the sentence “It is not clear whether these effects reflect a drug effect on the uterine environment or on the conceptus.”
e. Under the *Impairment of Fertility* section, added the sentence “This animal dose level of 100 Units/kg per day the clinical recommended start dose, depending on the patient’s treatment indication, but may be lower than the clinical dose in patients whose doses have been adjusted.”

4. Under Section 13 *Nonclinical Toxicology*, subsection 13.3 *Reproductive and Developmental Toxicology*:

   a. Added a sentence to the summary of the pre/postnatal study.

   **NOTE:** This change is important because the study was not designed to isolate effects in the offspring resulting from *in utero* exposure from effects in the offspring potentially due to exposure to Epoetin alfa via lactation.

   b. Added a sentence.

5. **NOTE:** The most recent previously published versions (i.e. 2/16/2010 and earlier) of the label included a paragraph relevant to nonclinical data under *PRECAUTIONS*:

   “In preclinical studies in dogs and rats, but not in monkeys, PROCRIT® therapy was associated with subclinical bone marrow fibrosis. Bone marrow fibrosis is a known complication of CRF in humans and may be related to secondary hyperparathyroidism or unknown factors. The incidence of bone marrow fibrosis was not increased in a study of adult patients on dialysis who were treated with PROCRIT® for 12 to 19 months, compared to the incidence of bone marrow fibrosis in a matched group of patients who had not been treated with PROCRIT®.”

   This information does not appear in the current version of the label; FDA had previously agreed to it’s removal (i.e. this wording does not appear in the 10/24/2008 FDA proposed revisions to the PLR label). The Nonclinical discipline defers to the Division of Medical Imaging and Hematology Products (DMIHP) Clinical review discipline regarding the overall importance of this section for physicians and patients.

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1 Accessed online via:

http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103234s5199lbl.pdf

http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103234s5232LBL.pdf
1.3.2 Selected sections of the PLR label proposed by Amgen

This version of the label was provided to reviewers 11/05/2009. The emphasis (highlighting) of the revisions that appear in this review were not conveyed.

"8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
The multidose formulation contains benzyl alcohol. (b)(4)

Pregnancy Category C (single-dose formulation only)

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.
8.3 Nursing Mothers

It is not known whether Epogen is excreted in human milk.

... 

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenic potential of Epogen has not been evaluated. Epogen does not induce bacterial gene mutation (Ames Test), chromosomal aberrations in mammalian cells, micronuclei in mice, or gene mutation at the HGPRT locus.

13.3 Reproductive and Developmental Toxicology

Postnatal observations of the live offspring (F1 generation) of female rats treated with Epogen during gestation and lactation revealed no effect of Epogen at doses of up to 500 Units/kg. There were no Epogen-related effects on the F2 generation fetuses."
1.3.3 Current FDA proposed version of the PLR label:

These proposed changes were conveyed to the sponsor 3/10/2010.

"8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

The multidose vials are formulated with benzyl alcohol.

Pregnancy Category C (single-dose vials only)
There are no adequate and well-controlled studies of Epogen use during pregnancy. There are limited data on use in pregnant women. In animal reproductive and developmental toxicity studies, adverse fetal effects occurred when pregnant rats received epoetin alfa at doses approximating the clinical recommended start doses. Single-dose formulations of Epogen should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

There are reports of at least 33 pregnant women with anemia alone or anemia associated with severe renal disease and other hematologic disorders who received Epogen. Polyhydramnios and intrauterine growth restriction were reported in women with chronic renal disease, which is associated with an increased risk for these adverse pregnancy outcomes. There was 1 infant born with pectus excavatum and hypospadias following exposure during the first trimester. Due to the limited number of exposed pregnancies and multiple confounding factors (such as underlying maternal conditions, other maternal medications, and gestational timing of exposure), these published case reports and studies do not reliably estimate the frequency or absence of adverse outcomes.

When healthy rats received Epogen at doses of 100 Units/kg per day during mating and through early pregnancy (dosing stopped prior to organogenesis), there were slight increases in the incidences of pre-and post-implantation loss, and a decrease in live fetuses. This animal dose level of 100 Units/kg per day the clinical recommended start dose, depending on the treatment indication. When healthy pregnant rats received Epogen at doses of 500 Units/kg per day late in pregnancy (after the period of organogenesis), offspring had decreased number of caudal vertebrae and growth delays.
Patients or their physicians should call 1-800-772-6436 (1-800-77-AMGEN) to enroll.

8.3 Nursing Mothers

The multidose vials of Epogen are formulated with benzyl alcohol; do not administer Epogen from multidose vials.

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 from single-dose vials to nursing women.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

The carcinogenic potential of Epogen has not been evaluated.

Mutagenicity

Epogen was not mutagenic or clastogenic under the conditions tested: Epogen was negative in the in vitro bacterial reverse mutation assay (Ames test), the in vitro mammalian cell gene mutation assay (the hypoxanthine-guanine phosphoribosyl transferase [HGPRT] locus) in an in vitro chromosomal aberration assay in mammalian cells, and in the in vivo mouse micronucleus assay.

Impairment of Fertility

When administered intravenously to male and female rats prior to and during mating, and to females through the beginning of implantation (up to gestational day 7; dosing stopped prior to the beginning of organogenesis), doses of 100 and 500 Units/kg per day of Epogen caused slight increases in pre-implantation loss, post-implantation loss and decreases in the incidence of live fetuses. It is not clear whether these effects reflect a drug effect on the uterine environment or on the conceptus. This animal dose level of 100 Units/kg per day is the clinical recommended start dose, depending on the patient's treatment indication, but may be lower than the clinical dose in patients whose doses have been adjusted.
13.2 Reproductive and Developmental Toxicology

When Epogen was administered intravenously during the period of organogenesis to pregnant rats (gestational days 7 to 17) and pregnant rabbits (gestational days 6 to 18), no evidence of teratogenic outcome was observed at the doses tested, up to 500 Units/kg per day. The offspring (F1 generation) of the treated rats were observed postnatally; rats from the F1 generation reached maturity and were mated; no Epogen-related effects were apparent for their offspring (F2 generation fetuses).”

2 Drug Information

2.1 Drug

2.1.1 CAS Registry Number: 11096-26-7

2.1.2 Generic Name: Erythropoietin, Epoetin alfa

2.1.3 Trade Name Epogen ®, Procrit ®

2.1.7 Pharmacologic class: erythropoiesis-stimulating agent (ESA)

2.2 Relevant IND/s, NDA/s, and DMF/s

BLA 103234 resulted in initial U.S. approval of Epogen/Procrit on June 1, 1989.
The most recent published label is posted at Drugs@FDA, dated 2/16/2010.
Supplement 5166 to BLA 103234 was submitted to the CDER electronic
document room (EDR), accessible via:
\cbsap5\mleCTD_Submissions\STN103951\103951.enx
   - This reviewer verified that no new nonclinical data were submitted in the
     CDER EDR.
This reviewer accessed the available electronic legacy data via the CBER EDR
   - This reviewer verified that no FDA nonclinical reviews were available in
     the CBER EDR.
   - This reviewer verified that no nonclinical data relevant to genetic toxicity or
     the developmental and reproductive toxicity (DART) were available in the
     CBER EDR.
As a parallel attempt to resolve the CR nonclinical issue, this reviewer attempted
   to find relevant documents in the archival paper copy of the BLA. Two of the
   DART study reports were retrieved, but no FDA review was identified.
This reviewer verified that no FDA nonclinical reviews were publicly available via
   Drugs@FDA. Notably, other disciplines' reviews are available for:
   - The 7/26/1999 action on supplement #1046
   - The 5/21/2004 action on supplement #5003.
   - The 6/30/2004 action on supplement #5043.
   - The 11/10/2004 action on supplement #5076.
   - The 10/26/2005 action on supplement # 5093.
MEMORANDUM

TO: The file
FROM: Andrew J. McDougal, Ph.D., D.A.B.T.
       Toxicologist. Pharmacology/Toxicology Branch, Division of Biologic Oncology Products (DBOP), Office of Oncology Drug Products (OODP), CDER. HFD-107.

THROUGH: Anne M. Pilaro, Ph.D., Acting Supervisory Toxicologist
          Pharmacology/Toxicology Branch, DBOP, OODP, CDER. HFD-107.

BLA #s:  103234/5166 (Epogen/Procrit) and 103951/5173 (Aranesp)
SPONSOR: Amgen, Inc.
PRODUCT: Darbepoetin alfa (Aranesp) and Epoetin alfa (Epogen/Procrit)

AMENDMENT TYPE: Prior Approval Supplement (PAS) / Physician Labeling Rule (PLR) Supplement

DATE: 10/20/2008

SYNOPSIS:

The DBOP Pharmacology/Toxicology Branch (P/T) concurs with the P/T Division of Medical Imaging and Hematology (DMIHP) review conducted by Dr. Yanli Ouyang (HFD-160). DBOP P/T has no further additions to or comments regarding the labeling.

This reviewer did not review new primary nonclinical data in support of these PLR supplements.
MEMORANDUM

To: BLA 103234/5166

From: Yanli Ouyang, MD, PhD, DABT, Toxicologist

Through: Adebayo Laniyonu, PhD, Supervisory Interdisciplinary Scientist

Date: October 19, 2008

Product: Epogen® (epoetin alfa)

Sponsor: Amgen Inc.

Re: sBLA and PLR labeling

The purpose of this memo is to communicate the nonclinical pharmacology and toxicology review status for the above sBLA. No new nonclinical pharmacology and toxicology study report was submitted for this sBLA. The reviewer has reviewed PLR labeling and participated PLR labeling meetings. Further review of PLR labeling may be needed upon receiving the sponsor's response.