CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103951Orig1s5173

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 103951/5173 ; 103951\5173\5010
Supporting document/s:	Electronic submission; PLR label
Applicant's letter date:	10/23/2009
Product:	Darbepoetin alfa (Aranesp)
Indication:	Aranesp is indicated for the treatment of anemia.
Applicant:	Amgen, Inc.
Amendment type	Physician Labeling Rule (PLR) Supplement eCTD sequence number: 0309 FDA receipt date 10/26/2009
Review Division:	Division of Hematology Products (DHP), Office of Oncology Drug Products (OODP)
Reviewer:	Yanli Ouyang, MD, PhD, DABT Yanli Ouyang 3/25/10
Supervisor:	Haleh Saber, Ph.D H. Saber 3/25/2010
Division Director:	Ann Farrell, MD
Project Manager:	Ebla Ali Ibrahim, MS

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 Aranesp 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.

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 103951/5173 ; 103951/5173/5010
Supporting document/s:	Accessed electronically via: \\cbsap58\M\eCTD_Submissions\STN103951\103951.enx
Product:	Darbepoetin alfa (Aranesp)
Indication:	Aranesp is an erythropoiesis-stimulating agent (ESA) indicated for the treatment of anemia due to: o Chronic renal failure (CRF) in patients on dialysis and patients not on dialysis o The effects of concomitant myelosuppressive chemotherapy that will be administered for a minimum of two additional months in patients with non-myeloid malignancies
Applicant:	Amgen, Inc.
Amendment type	Physician Labeling Rule (PLR) Supplement eCTD sequence number: 0309 FDA 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 Andrew Mc Dougal
Supervisor/Team Leader:	Anne M. Pilaro, Ph.D. HFD-107 March 24, 2010
Division Director:	Patricia Keegan, M.D.
Project Manager:	Mona Patel, Phrm.D.

TABLE OF CONTENTS

1 Executive Summary

1.1 Recommendation on Approvability

From a nonclinical perspective, approval is recommended.

1.2 Previous Communication with the Sponsor and Responses:

On 10/24/2008, a complete response letter was sent (Keegan/Shamon-Taylor). 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 toxicity 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."

The sponsor submitted 5 of 8 nonclinical study reports to the EDR on 10/28/2009. This reviewer was able to retrieve the original study reports from the FDA document room, as well as the original FDA/CBER review of these studies (Serabian, 8/23/2000; also publicly available via Drugs@FDA). Retrieval of these study reports resolves the nonclinical issue identified in the 10/24/2008 CR letter. The sponsor proposed revised language (please see below).

These study reports were considered for the PLR conversion, but were not fully re-reviewed. The following is the list of the nonclinical developmental and reproductive toxicity (DART) studies reviewed by Serabian (8/23/2000):

1. Study of Fertility & Early Embryonic Development to Implantation in the Rat with NM321 via IV Injection; study #970001
2. Study of Fertility & Early Embryonic Development to Implantation in the Rat with NM321 via IV Injection; study #970141

3. Study of Fertility & Early Embryonic Development to Implantation in the Rat with NM321 via IV Injection; study #100136
4. A Combined Range-Finding Developmental Toxicity & TK/Placental Transfer Study in Rats with NM321 when Administered iv; study #960124
5. A Developmental Toxicity Study with NM321 in the Rat via IV Injection; study #970024
6. A Range-Finding Developmental Toxicity Study of NM321 in the Rabbit via IV Injection; study #970009
7. A Developmental Toxicity Study with NM321 in the Rabbit via IV Injection; study #970023
8. Study Effects on Pre- and Postnatal Development Including Maternal Functions in Rats with NM321 via IV Injection; study #970075

Subsequently this reviewer was also able to access the EDR and retrieve electronic copies of the 5 submitted studies. The sponsor did not submit study #97001 or #100136, but did submit studies # 970141, 960124, 970024 and 970023. Because study 97001 and #100136 were preliminary experiments, this reviewer concurs that their omission from the 10/28/2009 response was acceptable.

This reviewer verified that NM321 is darbepoetin alfa.

1.3 Labeling

No new nonclinical data were submitted or reviewed. All nonclinical recommendations for changes to the darbepoetin 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 darbepoetin alfa in the nonclinical DART studies versus the recommended patient dose were revised to reflect label updates to the patient dosage information.

NOTE: One issue of potential confusion was considered internally. After discussion with the review team, the issue was addressed by adding the word "healthy" in Section 8.1 to describe the nonclinical models. Briefly:

- The FDA/CBER nonclinical review of the original BLA (Serabian, 8/23/2000) clearly acknowledges that the doses selected for the nonclinical DART studies were based on the results of repeat-dose toxicity studies which identified both the lethal dose of erythropoietin and the maximally tolerated dose (MTD).
- After dose adjustment, some patients receive doses that exceed the nonclinical lethal dose and the highest tested DART dose.

- This reviewer concludes that the apparent difference in tolerability may be due to disease status (i.e. doses that are pharmacologically active in patients with anemia may be toxic in healthy animals). Based on the availability of human data, additional nonclinical testing (i.e. in an anemic model) is not warranted.
- The finding that doses received by healthy animals may not be directly relevant to patients with anemia is a potential issue for clarification for the nonclinical portions of the label.
- This issue is mitigated by the sponsor's language in the PLR label indicating the doses at which signs of exaggerated pharmacology were observed in animals receiving darbepoetin alfa.

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. mcg/kg), and related the nonclinical doses to the range of patient starting doses (see below).

Although PK results were available from the DART studies, the review team decided against extrapolating the dose comparisons based on PK. This approach was considered potentially confusing because (a) it is not clear that the PK methods differentiated endogenous erythropoietin from administered darbepoetin alfa, (b) the context of the expected impact of disease status on PK and (c) because of the variability observed with the human PK results. In section 12.3 *Pharmacokinetics* of the current revised label, data are provided describing the magnitude of differences in PK due to age (i.e. adult CRF versus pediatric CFR) and indication (i.e. CRF and adult cancer).

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 doses are further complicated by recommendations to adjust dosing based on outcome. This table was extracted from the proposed PLR label information:

Patient population	**Recommended start doses**	**Dosing adjustment recommendations?**
Chronic renal failure patients	o 0.45 mcg/kg weekly for patients on hemodialysis o (b) (4) for patients not on dialysis	Yes
Cancer patients on chemotherapy	o 2.25 mcg/kg every week o 500 mcg/kg every 3 weeks	Yes

1.3.1 Nonclinical recommendations for label changes

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

1. Under Section 8 *Use in Specific Populations*, subsection 8.1 *Pregnancy*:

    a. Added the word "healthy" to describe the test model.
    b. Removed the wording that detailed the days of gestation for which the rats and rabbits were dosed. This information is appropriate for Section 13, but not for Section 8.1.
    c. Added "This animal dose level of 20 mcg/kg/day is (b) (4) higher than the clinical recommended start dose, depending on the patient's treatment indication, (b) (4)
    d. Added "This dose of 1 mcg/kg is near the clinical recommended starting dose."
    e. Added "While no adverse effects on uterine implantation occurred in animals, there was an increase in early post-implantation loss in animal fertility studies. It is not clear whether the increased post-implantation loss reflects a drug effect on the uterine environment or on the conceptus." (b) (4)

2. Under Section 13 *Nonclinical Toxicology*, subsection 13.1 *Carcinogenesis, Mutagenesis, Impairment of Fertility*:

    a. Revised the *Mutagenesis* section to begin with a summary sentence, "Aranesp was not mutagenic or clastogenic under the conditions tested."

    b. Revised the Impairment of Fertility Section to begin with the key finding, "Aranesp increased the incidence of post-implantation losses in rats."

    c. Under the *Impairment of Fertility* section, added the sentence "The dose of 10 mcg/kg is more than 10-fold higher than the clinical recommended staring dose (b) (4) ."

    d. Under the *Impairment of Fertility* section, added the sentence "The dose of 0.5 mcg/kg is approximately equivalent to the clinical recommended starting dose."

    e. Under the *Impairment of Fertility* section, added "Signs of exaggerated pharmacology were not observed in the mothers receiving 0.5 mcg/kg or less, but were observed at 2.5 mcg/kg and higher." This information is

new, and allows readers to more easily compare this section of the label with the information presented in Section 13.3.

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

   a. Added "This animal dose level of 20 mcg/kg/day is (b) (4) higher than the clinical recommended start dose, depending on the patient's treatment indication, (b) (4) ."

   b. Revised "No significant placental transfer of Aranesp was observed in rats" to "No significant placental transfer of Aranesp was observed in rats; placental transfer was not evaluated in rabbits." Additionally, this sentence formated as a stand-alone paragraph.

   c. Changed the description of study #970075 from (b) (4) development study" to "peri/postnatal development study"

   d. Added wording to clarify the meaning of F1 and F2 generation. The sentence now reads "The offspring (F1 generation) of the treated rats were observed postnatally; rats from the F1 generation reached maturity and were mated; no (b) (4) effects were apparent for their offspring (F2 generation fetuses).

1.3.2 Selected sections of the PLR label proposed by Amgen

This version of the label was received November 2009.

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

(b) (4)

2 Drug Information

2.1 Drug

2.1.1 CAS Registry Number: 11096-26-7

2.1.2 Generic Name: Erythropoietin,

Darbepoetin alfa

2.1.3 Trade Name Aranesp ®

2.1.7 Pharmacologic class: erythropoiesis-stimulating agent (ESA)

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

BLA 103951 resulted in initial U.S. approval of Aranesp on 9/17/2001.

- The most recent published label is posted at Drugs@FDA, dated 2/16/2010.
- Supplement 5173 to BLA 103951 was submitted to the CDER electronic document room (EDR), accessible via: \\cbsap58\M\eCTD_Submissions\STN103951\103951.enx
- This reviewer accessed the available electronic legacy data via 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.
- This reviewer accessed the archival paper copy of the BLA, to search for relevant nonclinical information.
  - The FDA primary review of the key nonclinical studies was identified.
  - The sponsor's summaries of the nonclinical sections were not identified.
- This reviewer identified one FDA nonclinical review publicly available via Drugs@FDA, the nonclinical review of the original BLA (Serabian 8/23/2000); this review is the same (although redacted) as was found in the archive.

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 #: 103951/5173/5010
SPONSOR: Amgen, Inc.
PRODUCT: darbepoietin alfa (Aranesp®, erythrocyte stimulating factor)
SUBMISSION TYPE: supplemental BL A 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 darbepoietin alfa (Aranesp®), 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. McDougal, 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. McDougal'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. McDougal'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.

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 103951/5173

From: Yanli Ouyang, MD, PhD, DABT, Toxicologist 10/20/08

Through: Adebayo Laniyonu, Ph.D. Supervisory Interdisciplinary Scientist 10/20/08

Date: October 19, 2008

Product: Aranesp® (darbepoetin 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.