CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103951Orig1s5173

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

BLA Number:	STN 103951/5173	**Submission Date:** 12/26/07
Product Name:	Aranesp (Darbepoetin)	
Route of Administration:	Subcutaneous (s.c.) injection	
Proposed Indication:	Anemia	
Submission Type:	SLR	
Sponsor:	Amgen	
Reviewer:	Aakanksha Khandelwal, Ph.D.	
Team Leader:	Hong Zhao, Ph.D.	

Introduction

The purpose of this submission is to convert the original labeling for Aranesp® (darbepoetin) to the new PLR (Physicians Labeling Rule) format.

Summary of darbepoetin label changes:

Original version of label provided by the sponsor with FDA recommended changes:

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

We recommend that the sponsor use median values instead of mean values when discussing half-life and peak concentrations due to the large range in values.

10/20/08

Aakanksha Khandelwal, Ph.D.
Reviewer
CDER/OTS/OCP/DCP5

10/20/08

Hong Zhao, Ph.D.
Team Leader
CDER/OTS/OCP/DCP5

Office of Clinical Pharmacology
NDA/BLA Filing and Review Form

General Information About the Submission

	Information		Information
BLA Number	STN 103951/5173, (b) (4)	Brand Name	Aranesp
OCP Division	DCP 5	Generic Name	Darbepoetin alfa
Medical Division	DBOP	Drug Class	Biologics
OCP Reviewer	Hong Zhao	Indication(s)	Anemia
OCP Team Leader/Division Director	Hong Zhao / Atik Rahman	Dosage Form	Injection solution
		Dosing Regimen	Weekly, Biweekly
Date of Submission	12/20/2008	Route of Administration	IV, SC
Estimated Due Date of OCP Review	8/28/2008	Sponsor	Amgen
PDUFA Due Date	10/28/2008	Priority Classification	S
Division Due Date	8/28/2008		

Clin. Pharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x	9		Only a few studies had PK data collected
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	x			
Dose proportionality -	x			
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				

PD:				
Phase 2:	x			
Phase 3:	x			
PK/PD:				
Phase 1 and/or 2, proof of concept:	x			
Phase 3 clinical trial:	x			
Population Analyses -				
Data rich:				
Data sparse:	x			
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
In-Vitro Release BE				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	x			
Total Number of Studies	9			

Filability and QBR comments

	"X" if yes	Comments
Application filable?	x	
Comments sent to firm?	none	
QBR questions (key issues to be considered)	1. **What are the PK characteristics of Darbepoetin alfa observed over the 12 weeks of dosing in Study NESP980291?** 2. **What is the dose-response relationship between doses of 4.5 and 12 mcg/kg for the hemoglobin response and mean change in hemoglobin endpoints?** 3. **What is the incidence of immunogenicity of Aranesp?** 4. **What is the risk-benefit ratio for using ESAs in Small-Cell Lung Cancer (SCLC) patient population and in populations with other cancer types?**	
Other comments or information not included above	**none**	
Primary reviewer Signature and Date	**Zhao, Hong** Hong Zhao 2/15/08	
Secondary reviewer Signature and Date	**Nam Atiqur Rahman** Atiqur Rahman 2/15/08	

CC: NDA/BLAXXX, HFD-850(Electronic Entry or Lee), HFD-107(CSO), HFD-860(TL, DD, DDD), CDR (B. Murphy)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

BLA	**STN 103951/5173/309**
Submission Date(s)	**October 23, 2009**
PDUFA Due Date	**April 27, 2010**
Brand Name	**Aranesp®**
Generic Name	**Darbepoetin alfa**
Reviewer	**Aakanksha Khandelwal, Ph.D.**
Team Leader	**Hong Zhao, Ph.D.**
OCP Division	**DCP 5**
OND Division	**OODP/DBOP**
Sponsor	**Amgen**
Submission Type	**Labeling supplement (PLR Conversion- Resubmission)**

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1. EXECUTIVE SUMMARY

Aranesp® (darbepoetin alfa) was approved by the FDA on September 17, 2001 for the treatment of anemia associated with chronic renal failure including both patients on dialysis and those not on dialysis.

In this labeling resubmission, the sponsor is proposing to convert the Aranesp® label to PLR (Physician's Labeling Rule) format. There is no new data or new studies included in this submission from a clinical pharmacology standpoint. The Clinical Pharmacology related changes are made to the following sections:

- Sections: 7 Drug Interactions updated to reflect standard labeling language
- 12.3 Pharmacokinetics has been updated to enhance clarity

See FDA recommended modifications below.

1.1 Recommendations

The application is acceptable from a clinical pharmacology perspective provided that the applicant agrees to the labeling recommendations.

2/4/10

Aakanksha Khandelwal, Ph.D.
Reviewer
CDER/OTS/OCP/DCP5

2-4-10

Hong Zhao, Ph.D.
Team Leader
CDER/OTS/OCP/DCP5

2. DETALIED LABELING RECOMMENDATIONS

2.1 Sponsor Proposed Labeling Changes and FDA Revisions

FDA recommended changes are made to the following sections of the label as shown below.

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