

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**103234Orig1s5166**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

**OFFICE OF CLINICAL PHARMACOLOGY REVIEW**

<b>BLA</b>	<b>STN 103234/5166</b>
<b>Submission Date(s)</b>	<b>October 23, 2009</b>
<b>PDUFA Due Date</b>	<b>April 27, 2010</b>
<b>Brand Name</b>	<b>Epogen® / PROCRIT®</b>
<b>Generic Name</b>	<b>Epoetin alfa</b>
<b>Reviewer</b>	<b>Aakanksha Khandelwal, Ph.D.</b>
<b>Team Leader</b>	<b>Hong Zhao, Ph.D.</b>
<b>OCP Division</b>	<b>DCP 5</b>
<b>OND Division</b>	<b>OODP/DBOP</b>
<b>Sponsor</b>	<b>Amgen</b>
<b>Submission Type</b>	<b>Labeling supplement (PLR Conversion) resubmission</b>

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## 1. EXECUTIVE SUMMARY

Epogen® and PROCRT® (epoetin alfa) were approved by the FDA on June 1, 1989 for the indication of anemia associated with chronic renal failure.

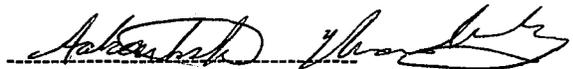
In this labeling submission, the sponsor is proposing to convert the Epogen® and PROCRT® labels to PLR (Physician's Labeling Rule) format. There is no new data or new studies included in this submission. The Clinical Pharmacology related changes are made to the following sections:

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

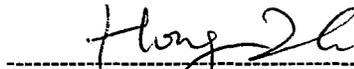
See FDA recommended modifications below.

### 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. DETAILED 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.

#### 6.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Neutralizing antibodies to epoetin alfa that cross-react with endogenous erythropoietin and other ESAs can result in PRCA or severe anemia (with or without other cytopenias) [see Warnings and Precautions (5.6)].

Deleted:

(b) (4)

Where reported, the incidence of antibody formation is highly dependent on the sensitivity and 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 PROCRIT with the incidence of antibodies to other products may be misleading.

#### DRUG INTERACTIONS

No formal drug interaction studies have been conducted with PROCRIT.

Deleted: (b)

Deleted:

(b) (4)

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

PROCRIT stimulates erythropoiesis by the same mechanism as endogenous erythropoietin.

### 12.2 Pharmacodynamics

PROCRIT increases the reticulocyte count within 10 days of initiation, followed by increases in the RBC count, hemoglobin, and hematocrit, usually within 2 to 6 weeks. The rate of hemoglobin increase varies among patients and is dependent upon the dose of PROCRIT administered. For correction of anemia in hemodialysis patients, a greater biologic response is not observed at doses exceeding 300 Units/kg 3 times weekly.

### 12.3 Pharmacokinetics

In adult and pediatric patients with CRF, the elimination half-life ( $t_{1/2}$ ) of plasma erythropoietin after intravenously (IV) administered PROCRIT ranged from 4 to 13

## Clinical Pharmacology Review

**Submission Date:** 12/26/07

**BLA Number:** STN 103234/5166  
**Product Name:** Procrit and Epogen (Epoetin alfa)  
**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 Procrit® and Epogen® to the new PLR (Physicians Labeling Rule) format.

### **Summary of epoetin alfa labeling changes:**

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

The following represents the final FDA recommended clinical pharmacology section of the label:

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Epogen stimulates erythropoiesis by the same mechanism as endogenous erythropoietin [see Description (11)].

### 12.2 Pharmacodynamics

Epogen increases the reticulocyte count within 10 days of initiation, followed by increases in the RBC count, hemoglobin, and hematocrit, usually within 2 to 6 weeks. The rate of hemoglobin increase varies among patients and is dependent upon the dose of Epogen administered. A greater biologic response is not observed at doses exceeding 300 Units/kg 3 times weekly (b) (4). Other factors affecting the rate and extent of response include availability of iron stores, (b) (4) and the presence of concurrent medical problems.

### 12.3 Pharmacokinetics

In adult and pediatric patients with CRF, the elimination half-life ( $t_{1/2}$ ) of plasma erythropoietin after intravenously administered Epogen ranges from 4 to 13 hours. After subcutaneous administration, peak plasma levels are achieved within 5 to 24 hours. The  $t_{1/2}$  is similar between adult patients with serum creatinine level greater than 3 and not on dialysis and those maintained on dialysis. The pharmacokinetic data indicate no apparent difference in Epogen  $t_{1/2}$  among adult patients above or below 65 years of age.

A pharmacokinetic study comparing 150 Units/kg subcutaneous 3 times weekly to 40,000 Units subcutaneous weekly dosing regimen was conducted for 4 weeks in healthy subjects ( $n = 12$ ) and for 6 weeks in anemic cancer patients ( $n = 32$ ) receiving cyclic chemotherapy. There was no accumulation of serum erythropoietin after the 2 dosing regimens during the study period. The 40,000 Units weekly regimen had a higher maximum concentration (3- to 7-fold), longer  $T_{max}$  (b) (4) (2- to 3-fold), higher area under the curve (1-168 hours) (2- to 3-fold) of erythropoietin and lower clearance (50%) than the 150 Units/kg 3 times weekly regimen. In anemic cancer patients, the average  $t_{1/2}$  was similar (40 hours with a range of 16 to 67 hours) after both dosing regimens. After the 150 Units/kg 3 times weekly dosing, the values of  $T_{max}$  and clearance were similar ( $13.3 \pm 12.4$  vs. 14.2

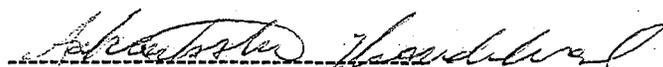
$\pm 6.7$  hours, and  $20.2 \pm 15.9$  vs.  $23.6 \pm 9.5$  mL/h/kg) between week 1 when patients were receiving chemotherapy (n = 14) and week 3 when patients were not receiving chemotherapy (n = 4). Differences were observed after the 40,000 Units weekly dosing with longer  $T_{max}$  ( $38 \pm 18$  hours) and lower clearance ( $9.2 \pm 4.7$  mL/h/kg) during week 1 when patients were receiving chemotherapy (n = 18) compared with those ( $22 \pm 4.5$  hours,  $13.9 \pm 7.6$  mL/h/kg, respectively) during week 3 when patients were not receiving chemotherapy (n = 7).

The pharmacokinetic profile of Epogen in children and adolescents appears to be similar to that of adults. Limited data are 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.

The pharmacokinetics of Epogen have not been studied in HIV-infected patients.

### Recommendations

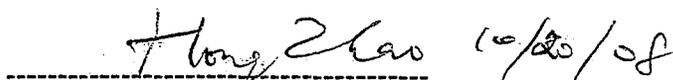
We do not have any further clinical pharmacology related recommendations at this time.

 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 103234/5166 (b) (4)	Brand Name	Epogen/Procrit
OCP Division	DCP5	Generic Name	Epoetin 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	Single-dose preservative-free vial
		Dosing Regimen	TIW
Date of Submission	12/20/2008	Route of Administration	SC or IV
Estimated Due Date of OCP Review	8/28/2008	Sponsor	Amgen
PDUFA Due Date	10/28/2008	Priority Classification	S
Division Due Date			

**Clin. Pharm. Information**

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x	12		
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods				
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
<i>Patients-</i>				
single dose:				
multiple dose:	x			
Dose proportionality -				
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:				

**Part D – Clinical (Pharmacology, Efficacy, Safety, and Statistical) Reviewers**

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Introduction to the summary documents (1 page) [2.2]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Clinical overview [2.5]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Biopharmaceutics and associated analytical methods	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Clinical pharmacology [includes immunogenicity]	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Clinical Efficacy [for each indication]	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Clinical Safety	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Synopses of individual studies	<input checked="" type="radio"/> Y <input type="radio"/> N	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Tabular Listing of all clinical studies [5.2]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Study Reports and related information [5.3]	<input checked="" type="radio"/> Y <input type="radio"/> N	N/A
<input type="checkbox"/> Biopharmaceutic	<input type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Studies pertinent to Pharmacokinetics using Human Biomaterials	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Pharmacokinetics (PK)	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Pharmacodynamic (PD)	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Efficacy and Safety	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Postmarketing experience	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Case report forms	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Individual patient listings (indexed by study)	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> electronic datasets (e.g. SAS)	<input checked="" type="radio"/> Y <input type="radio"/> N	
Literature references and copies [5.4]	<input checked="" type="radio"/> Y <input type="radio"/> N	

Examples of Filing Issues	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> legible	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> English (or certified translation into English)	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> compatible file formats	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> navigable hyper-links	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	<input checked="" type="radio"/> Y <input type="radio"/> N	

Examples of Filing Issues	Yes?	If not, action & status
<input type="checkbox"/> summary reports reference the location of individual data and records	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> protocols for clinical trials present	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> all electronic submission components usable	<input checked="" type="radio"/> Y <input type="radio"/> N	
statement for each clinical investigation:		
<input type="checkbox"/> conducted in compliance with IRB requirements	<input type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> conducted in compliance with requirements for informed consent	<input type="radio"/> Y <input type="radio"/> N	<i>clinical</i>
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	<input type="radio"/> Y <input type="radio"/> N	<i>clinical</i>
<b>adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication</b>	<input type="radio"/> Y <input type="radio"/> N	<i>clinical</i>
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	<input type="radio"/> Y <input type="radio"/> N	<i>clinical</i>
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	<input type="radio"/> Y <input type="radio"/> N	<i>N/A</i>
<b>total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)</b>	<input type="radio"/> Y <input type="radio"/> N	<i>clinical</i>
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	<input type="radio"/> Y <input type="radio"/> N	<i>clinical</i>
drug interaction studies communicated as during IND review as necessary are included	<input type="radio"/> Y <input type="radio"/> N	<i>N/A</i>
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	<input checked="" type="radio"/> Y <input type="radio"/> N	<i>clinical</i>
comprehensive analysis of safety data from all current world-wide knowledge of product	<input checked="" type="radio"/> Y <input type="radio"/> N	

Examples of Filing Issues	Yes?		If not, action & status
data supporting the proposed dose and dose interval	Y	N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	Y	N	
adequate characterization of product specificity or mode of action	<input checked="" type="checkbox"/>	N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	Y	N	N/A
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y	N	N/A
all information reasonably known to the applicant and relevant to the safety and efficacy described?	<input checked="" type="checkbox"/>	N	

List of Clinical Studies (protocol number)	Final study report submitted?		Financial disclosure or certification submitted?			SAS & other electronic datasets complete & usable?		BiMo sites identified?		
	Y	N	Y	N	NR	Y	N	Y	N	NR
PK NESP 980291	<input checked="" type="checkbox"/>	N	Y	N	NR	Y	N	Y	N	NR
re-finding NESP 990114	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR

Y= yes; N=no; NR=not required

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

none

Is clinical site(s) inspection (BiMo) needed?

Defer to Clinical

Is an Advisory Committee needed?

Defer to Clinical

Recommendation (circle one): File RTF

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

Reviewer: Hoy Zhao Type (circle one): Clinical ClinPharm Statistical

Concurrence:

Branch Chief: \_\_\_\_\_ (signature/ date)

Division Director: Aliquis Sab 2/15/08 (signature/ date)