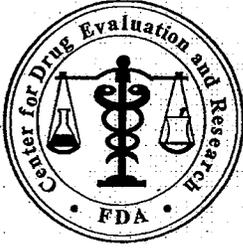


**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**BLA 125160/0**

**RISK ASSESSMENT and RISK MITIGATION  
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

Date: April 1, 2008  
To: Donna Griebel, M.D., Director  
Division of Gastroenterology Products (DGP)  
Through: Jodi Duckhorn, MA  
Patient Labeling and Education Team Leader  
Division of Risk Management (DRISK)  
From: Jeanine Best, MSN, RN, PNP  
Senior Drug Risk Management Analyst  
Division of Risk Management (DRISK)  
Subject: Medication Guide Review  
Drug Name(s): Cimzia (certilizumab pegol)  
Application Type/Number: BLA 125160/0  
Applicant/sponsor: UCB, Inc.  
OSE RCM #: 2007-1990

*Jodi Duckhorn*  
4/1/2008  
*Jeanine Best*  
4/1/08

## **1 INTRODUCTION**

UCB submitted a Complete Response submission for Cimzia (certilizumab pegol), BLA 125160/0, on April 30, 2007, in response to a Complete Response Letter issued December 21, 2006. Cimzia is a tumor necrosis factor (TNF) blocker indicated for reducing the signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.

Submitted labeling included Prescribing Information (PI) and Patient Labeling in the form of a Patient Package Insert (PPI). All TNF blocker products have been requested to replace their PPIs with Medication Guides because of the serious and significant public health concern of the risk of serious infections including tuberculosis. At the request of DGP, a Medication Guide was submitted September 10, 2007, to replace the PPI.

## **2 MATERIAL REVIEWED**

- Medication Guide submitted September 10, 2007, and revised versions submitted March 21 and 27, 2008
- Prescribing Information (PI – PLR format) submitted September 14, 2007, and revised versions submitted March 21 and 27, 2008

## **3 DISCUSSION AND RECOMMENDATIONS**

The Cimzia Patient Package Insert (PPI) was previously reviewed by OSE/DSRCS (see PPI Review dated September 28, 2006). Comments were not conveyed to the Sponsor during that review cycle.

- The Cimzia Medication Guide in conjunction with DGP/Sponsor labeling negotiations was:
  - revised to meet the Medication Guide regulations specified in 21 CF 208;
  - revised for consistency with revisions to the Prescribing Information
  - revised for consistency with other approved TNF blocker product MGs;
  - simplified to an 8<sup>th</sup> grade reading level (Flesch-Kincaid Reading Level).
- The draft Cimzia MG dated March 27, 2008, is acceptable to OSE/DRISK with one minor word revision under the section "What are the possible side effects with Cimzia?". The term " → " was revised to the consumer-friendly term of "joint pain". DGP conveyed this revision to the Sponsor on March 28, 2008.



## EXECUTIVE SUMMARY

The purpose of this review is to provide DSRCs' comments on the current proposed pharmacovigilance activities for certolizumab pegol (Cimzia®), an anti tumor necrosis factor alpha (TNF $\alpha$ ) agent, for \_\_\_\_\_

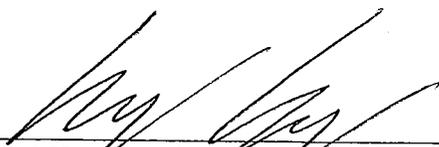
Based on DSRCs' review, the proposed additional pharmacovigilance activities, \_\_\_\_\_ lack sufficient detail for a thorough evaluation. Therefore, we were able to offer only preliminary comments on both proposals for the Sponsor's consideration. We have identified areas of deficiencies in the proposed \_\_\_\_\_ and have concerns regarding the proposed \_\_\_\_\_

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Draft Labeling

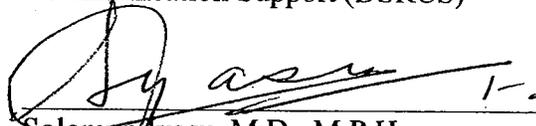
Deliberative Process



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Concurrence:  
Tarek Hammad, MD, PhD, MSc, MS  
Acting Team Leader  
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1-22-08

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Solomon Iyasu, M.D., M.P.H.  
Acting Director  
Division of Surveillance, Research and  
Communication Support (DSRCS)



MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** November 9, 2006

**TO:** Brian Harvey, M.D., Ph.D., Director  
Division of Gastrointestinal Products

**THROUGH:** Gerald Dal Pan, MD, MHS, Director  
Office of Surveillance and Epidemiology

**FROM:** OSE Certolizumab RMP Team

**DRUG:** Cimzia (Certolizumab Pegol)

**BLA#:** 125160

**SPONSOR:** UCB, Inc.

**SUBJECT:** Review of Proposed Risk Management Plan (RMP) submitted February 28, 2006

**RCM#:** 2006-666



## 1 INTRODUCTION/BACKGROUND

This consult follows a request from the Division of Gastrointestinal Products (DGP) for the Office of Surveillance and Epidemiology (OSE) to review and comment on the proposed Risk Management Plan (RMP) for certolizumab submitted with the Biologic Licensing Application.

Certolizumab pegol is a recombinant, humanized antibody Fab' fragment, with specificity for human tumor necrosis factor alpha (TNFa). The Fab' fragment is manufactured in *Escherichia coli* and is subsequently purified and conjugated to polyethylene glycol (PEG). The proposed indication is for \_\_\_\_\_

\_\_\_\_\_ . The proposed adult dose is an induction regimen of 400 mg given as two subcutaneous injections at weeks 0, 2, and 4, followed by a maintenance regimen of 400 mg every 4 weeks. Certolizumab is also being studied in rheumatoid arthritis and psoriasis patients.

Crohn's Disease treated with certolizumab at any dose. The Sponsor's safety summary<sup>1</sup> provides the following information:

- The most common adverse events were Crohn's disease (lack of improvement/disease progression), headache, and abdominal pain.
- Infections:
  - The overall incidence of infections in Crohn's disease trials were about 36% for certolizumab-treated at 400mg (41% at any dose) patients compared to 30% for placebo-treated patients. The most common infections were nasopharyngitis, urinary tract infections, upper respiratory tract infections, influenza, and gastrointestinal abscesses.
  - The incidence of serious infections was 2.5% for certolizumab-treated at 400mg (4.4% at any dose) patients and 1.4% for placebo-treated patients. Serious infections observed included: bacteremia, pneumonia, and pyelonephritis. There was one fatality due to pneumocystis carinii aveolitis.
  - A total of 13 cases of tuberculosis have been reported in all studies as of June 6, 2006.
- Malignancies:
  - In Crohn's disease clinical studies, the overall incidence of any malignancy was 0.5% in certolizumab-treated patients and 0.7% in placebo-treated patients. The only case of lymphoma occurred in a patient treated with placebo.
- Other AEs:
  - There were no cases of anaphylactic shock or clinically severe anaphylactic reactions reported in clinical studies.
  - A total of 218 hematological AEs were reported in 135 subjects; these events were reported to be serious in 15 subjects.
  - A total of 78 hepatobiliary AEs were reported in 44 subjects; these events were reported to be serious in 4 subjects. The overall incidence of hepatobiliary events was 2.7% in certolizumab-treated patients compared to 1.6% in placebo-treated patients.
  - A total of 13 pregnancies were reported in all certolizumab studies as of June 6, 2006. Of these 1 is ongoing, five resulted in full-term healthy babies (1 with intrauterine growth retardation), five were elective abortions, one resulted in miscarriage, and the pregnancy outcome in one is unknown.

The Sponsor's conclusion of their analysis of safety data is that the identified risks in clinical studies for certolizumab are known to be associated with anti-TNF mechanism of action and the types of adverse events are consistent with similar drugs of this category, although they concede the incidence may be different. At the time of this review, the Medical Officer clinical review had not been completed.

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<sup>1</sup> Source is Sponsor's proposed labeling and the 120-Day Safety Update dated 27 June 2006.

## 2 PROPOSED RMP

The Sponsor's RMP proposal includes routine pharmacovigilance activities as well as additional pharmacovigilance activities. The Sponsor does not believe the safety profile warrants a Risk Minimization Action Plan (RiskMAP).

### 2.1 *Routine Pharmacovigilance Practices*

The Sponsor proposes routine pharmacovigilance to collect additional data in populations that were excluded from study. They plan to capture experience on exposure during pregnancy using routine pharmacovigilance practices.

### 2.2 *Additional Pharmacovigilance Activities*



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       Draft Labeling

       Deliberative Process

**OSE Certolizumab RMP Review Team:**

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Cynthia Kornegay, Ph.D., Epidemiologist, DDRE

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Mary Willy, Ph.D., Senior Risk Management Analyst (detail), OSE-IO