

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993



STN: BL 125271/0

BLA APPROVAL
May 13, 2009

UCB, Inc.
1950 Lake Park Drive
Smyrna, GA 30080

Attention: Sandra Bonsall, RAC
Associate Director, Regulatory Affairs

Dear Ms. Bonsall:

Please refer to your biologics license application (BLA) dated November 29, 2007, received December 6, 2007, submitted under section 351 of the Public Health Service Act for CIMZIA[®] (certolizumab pegol).

We acknowledge receipt of your submissions dated February 15, March 14, April 3, May 16 and 30, July 18, August 11, 12, 14, 20, 25, and 28, September 3, 9, 10, 15, and 30, October 14 and 21, November 21, and December 12, 18, 19, 22, and 24, 2008, March 12, April 21 and 27, and May 12, 2009.

Your March 12, 2009, submission constituted a complete response our January 2, 2009 action letter.

We have completed our review of this application, as amended, and your biologics license application for CIMZIA (certolizumab pegol) is approved. You are hereby authorized to introduce or deliver for introduction into interstate commerce, CIMZIA (certolizumab pegol) under your existing Department of Health and Human Services U.S. License No. 1736. CIMZIA (certolizumab pegol) is indicated the for treatment of rheumatoid arthritis (RA).

Your application for CIMZIA (certolizumab pegol) was not referred to an FDA advisory committee because your product is a member of the class of tumor necrosis factor (TNF)-blockers and the safety and efficacy data did not pose unique concerns beyond those applicable to other biologic products approved for the treatment of rheumatoid arthritis.

Under this license, you are approved to manufacture certolizumab pegol drug substance at (b) (4). The final formulated product will be manufactured, filled, labeled, and packaged at (b) (4) and at (b) (4). You may label your product with the proprietary name CIMZIA (certolizumab pegol) and market it in 200 mg/mL sterile solution in pre-filled syringes.

The dating period for CIMZIA (certolizumab pegol) shall be 18 months from the date of manufacture when stored at 2 to 8 °C. The date of manufacture shall be defined as the date of (b) (4) of the formulated drug product. The dating period for your bulk drug substance shall be (b) (4). We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

You currently are not required to submit samples of future lots of CIMZIA (certolizumab pegol) to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/oc/datacouncil/spl.html>, that is identical to the enclosed labeling and Medication Guide. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission “**Product Correspondence – Final SPL for approved STN BL 125271/0.**”

Pursuant to 21 CFR 201.57(c)(18) and 201.80(f)(2), patient labeling must be reprinted immediately following the last section of labeling or, alternatively, accompany the prescription drug labeling.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the labels submitted on November 21, 2008, as soon as they are available but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Product Correspondence – Final Printed Carton and Container Labels for approved STN BL 125271/0.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with labeling that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of

administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to < 2 years because necessary studies are impossible or highly impracticable. This is because juvenile idiopathic arthritis (JIA) polyarticular subtype most often occurs in children age ≥ 2 years and older and is infrequent in children aged 0 to < 2 years of age.

We are deferring submission of your pediatric studies for ages ≥ 2 to < 17 years for this application because this product is ready for approval for use in adults and pediatric studies have not been completed.

Your deferred pediatric study required under section 505B(a) of the FDCA is a required postmarketing study. The status of this post-marketing study must be reported annually according to 21 CFR 301.70 and section 505B(a)(3)(B) of the FDCA. This required study is listed below.

1. Assessment of pharmacokinetic (PK/PD) parameters and dosing, safety, tolerance and immunogenicity in the pediatric population ≥ 2 years to < 17 years with polyarticular JIA.

Protocol Submission:	October 2009
Study Start Date:	December 2010
Final Report Submission:	October 2015

Submit final study reports to your BLA 125160. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated **“Required Pediatric Assessment.”**

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if the FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(1)).

Since the REMS for CIMZIA (certolizumab pegol) was modified on December 31, 2008 (BLA 125160), we are expanding the indicated population to include RA patients. Due to disease characteristics in the RA population, the extension of the indication to a new population changes the risk benefit profile of CIMZIA (certolizumab pegol) and is considered to be “new safety information” as defined in FDAAA.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that CIMZIA (certolizumab pegol) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The

Medication Guide is necessary for patients' safe and effective use of CIMZIA (certolizumab pegol). FDA has determined that CIMZIA (certolizumab pegol) is a product that has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use CIMZIA (certolizumab pegol). In addition, patient labeling could help prevent serious adverse effects related to the use of the product. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed CIMZIA (certolizumab pegol).

We have also determined that a communication plan is necessary to support implementation of the REMS.

Your proposed revisions to the approved REMS for CIMZIA, submitted on March 12, 2009 and appended to this letter, is approved. We are approving a single REMS for BLAs 125271 and 125160. The REMS consists of the Medication Guide, the communication plan, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include but not be limited to:

- a. Survey of patients' understanding of the serious risks of CIMZIA (certolizumab pegol).
- b. Report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
- c. Report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.
- d. Survey of physicians' understanding of the serious risks of CIMZIA (certolizumab pegol).

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), requirements for information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 601.70 and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify submissions containing REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission:

BLA 125271/125160 REMS ASSESSMENT

**NEW SUPPLEMENT FOR BLA 125271/125160
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR<<insert application #>>
REMS ASSESSMENT**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

Since the REMS for CIMZIA (certolizumab pegol) was modified on December 31, 2008, we are expanding the indicated population to include RA patients. Due to disease characteristics in the RA population, the extension of the indication to a new population changes the risk benefit profile of CIMZIA (certolizumab pegol) and is considered to be “new safety information” as defined in FDAAA."

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) will not be sufficient to assess the following long-term serious risks in adult patients with RA who are treated with CIMZIA (certolizumab pegol): (1) cardiovascular and thromboembolic events, including congestive heart failure, hypertension, transient ischemic attack (TIA), stroke, tachyarrhythmia, atrial fibrillation, venous thrombosis and phlebitis; (2) serious infections including opportunistic infections and (3) malignancies, both solid tumors and lymphomas.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following postmarketing clinical study:

2. An observational study registry in adult patients with moderately to severely active RA that would assess the longer term risks of serious infections, malignancies that have been reported with TNF α blocker therapy, as well as the longer term risk for cardiovascular and thromboembolic events, including

congestive heart failure, hypertension, TIA, stroke, tachyarrhythmia, atrial fibrillation, venous thrombosis and phlebitis.

The timetable you submitted on May 12, 2009 states that you will conduct this trial according to the following timetable:

Final Protocol Submission: August 2009
Study Completion Date: February 2010
Final Report Submission: February 2017

Submit the protocol to your IND 9,869, with a cross-reference letter to this BLA 125160. Submit all final reports to your BLA 125160. Prominently identify all submissions relating to this postmarketing study requirement with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING STUDY COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS OF 21 CFR 601.70

3. To re-evaluate the drug product sub-visible release and shelf-life specifications upon confirming the feasibility of a preparatory method that will enable implementation of the USP <788> preferred method. Data and specification assessment will be provided within 2 years from the time of approval.

Study Completion: January 2011
Final Report Submission: April 2011

4. To conduct additional studies to evaluate the process-specific assay test for the assessment of HCP per your May 12, 2009 submission. A summary report and data will be provided by June 30, 2009.

Study Completion: June 2009
Final Report Submission: July 2009

Submit clinical protocols to your IND, with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this BLA. Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing commitments, as appropriate:

- Postmarketing Commitment Protocol
- Postmarketing Commitment - Final Report
- Postmarketing Correspondence
- Annual Status Report of Postmarketing Commitments

For each postmarketing commitment not subject to the reporting requirements of 21 CFR 601.70, you may report the status to FDA as a “PMC Submission –Status Update.” The status report for each commitment should include:

- The original schedule for the commitment
- The status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted)

When you have fulfilled your commitment, submit your final report as PMC Submission – Final Report or Supplement Contains Postmarketing Commitment – Final Report.

PROMOTIONAL MATERIALS

You may submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit an electronic copy of the letter to both this BLA and to the following address:

MedWatch, HFD-001
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20852-9787

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to the following address:

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to the following address:

Division of Compliance Risk Management and Surveillance
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20903

Biological product deviations sent by courier or overnight mail should also be sent to this address.

You must submit information to your biologics license application for our review and written approval under 21 CFR 601.12 for any changes in the manufacturing, testing, packaging, or labeling of CIMZIA (certolizumab pegol) or in the manufacturing facilities.

All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original BLA 125160 for this drug product. In the future, do not make submissions to this BLA except for the final printed labeling requested above.

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, call Kathleen Davies, Regulatory Project Manager, at (301) 796-2205.

Sincerely,

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures (4):
Package Insert
Medication Guide
Carton and Immediate Container Labeling
REMS