



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

STN: BL 125271/0

BLA APPROVAL

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, January 15, March 12, and April 21, 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[®] under your existing Department of Health and Human Services U.S. License No. 1736. CIMZIA[®] is indicated for treatment of rheumatoid arthritis.

Your application for CIMZIA[®] 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 [REDACTED]. The final formulated product will be manufactured, filled, labeled, and packaged at [REDACTED] and at [REDACTED]. You may label your product with the proprietary name CIMZIA and will market it in 200 mg/mL sterile solution in pre-filled syringes.

The dating period for CIMZIA[®] 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 [REDACTED] (b) (4) of the formulated drug product. The dating period for your bulk drug substance shall be [REDACTED] (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[®] 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 July 18, 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 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. The adult RA exposure-response should form the basis for these dose simulations in pediatric patients.

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.”**

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize 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), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the following long-term serious risks in adult patients with RA with the use of CIMZIA (certolizumab pegol): (1) cardiovascular and thromboembolic events, including congestive heart failure, hypertension, transient ischemic attack (TIA), stroke, tachyarrhythmia, atrial fibrillation, venous thrombosis and associated 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:

1. A postmarketing clinical 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 associated phlebitis.

The timetable you submitted on December 17, 2008 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 9869, with a cross-reference letter to this BLA 125160. Submit all final report(s) to your BLA 125160. Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing study requirement 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 requires 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

2.

(b) (4)

3.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Title IX, Subtitle A, Section 901 of Food and Drug Administration Amendments Act of 2007 (FDAAA) amended the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if the Secretary determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(1)). This provision took effect on March 25, 2008.

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[®] 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[®]. FDA has determined that CIMZIA[™] 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[®]. 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[®].

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

Your proposed REMS is approved. The REMS consists of the Medication Guide, the communication plan included with this letter, and the timetable for submission of assessments of the REMS included in your March 12, 2009 submission.

Information needed for assessment of the REMS should include but not be limited to:

- a. Survey of patients' understanding of the serious risks of CIMZIA[®]

- 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®

Use the following designator to prominently label all submissions, including supplements, relating to this REMS:

Risk Evaluation and Mitigation Strategy (REMS)

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
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 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 (3):
Package Insert
Patient Package Insert
Carton and Immediate Container Labeling