

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**BLA 125160/0**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

Our STN: BL 125160/0

APR 22 2008

UCB, Inc.  
Attention: Patricia Fritz, M.S.  
Vice President, Global Regulatory Affairs  
1950 Lake Park Drive  
Smyrna, Georgia 30080

Dear Ms. Fritz:

We are issuing Department of Health and Human Services U.S. License No. 1736 to UCB, Inc., Smyrna, Georgia, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product CIMZIA™. CIMZIA™ is 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.

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 Crohn's disease including other members of this class and Tysabri (natalizumab), an alpha-4 integrin blocker.

Under this license, you are approved to manufacture CIMZIA™ drug substance at [redacted]. The final formulated product will be manufactured at [redacted], [redacted]. Commercial labeling and packaging will occur at UCB Manufacturing in Rochester, New York. You may label your product with the proprietary name CIMZIA™ and will market it in a pack containing 200 mg of lyophilized product.

The dating period for CIMZIA™ shall be 18 months from the date of manufacture when stored at 2-8 °C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be 12 months when stored at -70°C. The expiration date for the packaged product, CIMZIA™ plus the sterile Water for Injection diluent shall be dependent on the shortest expiration date of any component. We have approved the stability protocol(s) 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.

### **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 5 years because studies are impossible or highly impractical due to the small number of pediatric Crohn's disease patients less than 6 years of age.

We are deferring pediatric studies for ages 6 to 17 years because pediatric studies should be delayed until additional data from postmarketing studies in adults have been submitted.

Your deferred pediatric study required under section 505B(a) of the Federal Food, Drug and Cosmetic Act (FDCA) is a required pediatric postmarketing study. The status of this required pediatric postmarketing study must be reported annually according to 21 CFR 601.70 and section 505B(a)(3)(B) of the FDCA. This requirement is listed below:

1. Conduct a study in pediatric patients, "*A Phase II Open-Label Multi-Center Study to Assess the Safety and Efficacy of Certolizumab pegol in Children and Adolescents with Active Crohn's Disease*" [Study CDP870-035]. This study is proposed to evaluate the pharmacokinetics, safety and clinical response of pediatric patients, ages 6-17, with moderately to severely active Crohn's disease to treatment with CIMZIA™.

We acknowledge the timetable you submitted on April 8, 2008, which states that you will conduct this study according to the following schedule:

Protocol Submission:	September 2008
Study Start Date:	June 2009
Final Report Submission:	October 2013

Submit final study reports to this BLA, STN BL 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 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 the TNF blocker class, of which this product is a member, has been associated with known serious risks of serious infections, including opportunistic infections, development of lymphoma and other malignancies, and development of demyelinating disorders and autoimmune disorders in Crohn's disease patients. In addition, available data suggest that members of the TNF blocker class may impair a patient's ability to mount an appropriate immune response to B cell- and T cell-mediated immunization and thereby subject the patient to unexpected serious risks.

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 these known serious risks or to identify unexpected serious risks that, based on available data, have the potential to occur with CIMZIA™. 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 thus not sufficient to assess these known serious risks or identify whether CIMZIA™ is associated with unexpected serious risks.

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

2. A long-term observational study in the U.S. that will include approximately 2000 CIMZIA™-treated Crohn's disease patients and 2000 matched controls receiving other treatments for Crohn's disease. Patients will be monitored for ten years.

We acknowledge the timetable you submitted on April 8, 2008, which states that you will conduct this study according to the following schedule:

Protocol Submission:	September 2008
Study Start Date:	February 2009
Final Report Submission:	March 2020

In addition, we have determined that only clinical trials will be sufficient (rather than an observational study) to show whether a specific level of risk (occurrence of serious infections, including opportunistic infections, development of lymphoma and other malignancies, and development of demyelinating disorders and autoimmune disorders) can be predicted by measurement of pharmacokinetics and antibody responses in Crohn's disease patients receiving long-term treatment with CIMZIA™.

Therefore, based on appropriate scientific data, we have determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the postmarketing clinical trials described below. You are required to revise the protocols for the following three clinical trials to extend the period of patient follow-up from the start of treatment:

3. CDP870-033, an ongoing open-label trial to assess the long-term safety of CIMZIA™ in patients with Crohn's disease who have previously completed trials CDP870-031 or

CDP870-032. The objectives of this trial include measurement of pharmacokinetics and antibody response in CIMZIA™-treated patients. Patient follow-up will be extended to seven years from the start of treatment.

We acknowledge the timetable you submitted on April 8, 2008, which states that you will conduct this clinical trial according to the following schedule:

Protocol Amendment Submission:	October 2008
Trial Start Date:	Ongoing
Final Report Submission:	May 2013

4. CDP870-034, an ongoing open-label trial to assess the long-term safety of re-exposure to CIMZIA™ after a variable interval in patients with Crohn's disease who were previously withdrawn from completed trials CDP870-031 or CDP870-032 due to an exacerbation of Crohn's disease. The objectives of this trial include measurement of pharmacokinetics and antibody response in CIMZIA™-treated patients. Patient follow-up will be extended to seven years from the start of treatment.

We acknowledge the timetable you submitted on April 8, 2008, which states that you will conduct this clinical trial according to the following schedule:

Protocol Amendment Submission:	October 2008
Trial Start Date:	Ongoing
Final Report Submission:	May 2013

5. CDP870-088, an open-label trial to assess the long-term safety of CIMZIA™ in patients with Crohn's disease who have either completed trial CDP870-085 or were withdrawn from CDP870-085 due to an exacerbation of Crohn's disease. The objectives of this trial include measurement of pharmacokinetics and antibody response in CIMZIA™-treated patients. Patient follow-up will be extended to five years from the start of treatment.

We acknowledge the timetable you submitted on April 8, 2008, which states that you will conduct this clinical trial according to the following schedule:

Protocol Amendment Submission:	October 2008
Trial Start Date:	May 2008
Final Report Submission:	May 2015

Finally, we have determined that only a clinical trial will be sufficient (rather than an observational study) to assess post-vaccination antibody responses in CIMZIA™-treated patients and identify to what extent treatment affects response to B cell- and T cell-mediated immunization. Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following postmarketing clinical trial of CIMZIA™:

6. A placebo-controlled trial designed to assess the effects of CIMZIA™ treatment on antibody responses to a B cell-mediated immunization, using pneumococcal vaccine immunization, and to a T cell-mediated immunization, using influenza vaccine, in patients with active rheumatoid arthritis. The study will measure both antibody titers and rates of clinical response in approximately 100 placebo- and 100 CIMZIA™-treated patients who will be given polyvalent pneumococcal polysaccharide vaccine and influenza vaccine.

We acknowledge the timetable you submitted on April 8, 2008, which states that you will conduct this clinical trial according to the following schedule:

Protocol Submission:	October 2008
Trial Start Date:	October 2009
Final Report Submission:	March 2011

Please submit the protocols to your IND 11,197, with a cross-reference letter to this BLA, STN BL 125160. Submit all final reports to your BLA, STN BL 125160. Please use the following designators to prominently label all submissions, including supplements, relating to the postmarketing study and clinical trials described above as appropriate:

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

You are required to report periodically to FDA on the status of the postmarketing study and clinical trials described above pursuant to sections 505(o)(3)(E)(ii) and 506B of the FDCA, as well as 21 CFR 601.70. Under section 505(o)(3)(E)(ii), you are also required to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue associated with CIMZIA™.

#### **RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS**

Title IX, Subtitle A, Section 901 of FDAAA amends 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™.

Your proposed REMS is approved. The REMS consists of the Medication Guide included with this letter and the timetable for submission of assessments of the REMS included in your April 16, 2008 submission. The timetable you submitted is as follows:

1 <sup>st</sup> FDAAA assessment:	November 2009 (18 months from approval)
2 <sup>nd</sup> FDAAA assessment:	May 2011 (3 years from approval)
3 <sup>rd</sup> FDAAA assessment:	May 2015 (7 years from approval)

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

For administrative purposes, all submissions related to this REMS must be clearly designated as a "REMS Submission".

### **ADVERSE EVENT REPORTING**

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). We ask that you submit any adverse event reports related to malignancy, serious infections (including opportunistic infections and tuberculosis), serious hemorrhage, and serious skin reactions (e.g. Stevens Johnson's Syndrome, toxic epidermal necrosis and erythema multiforme) as 15-day reports, per reporting regulation 21 CFR 600.80. Serious events are defined as events leading to death, hospitalization, disability, or reported as life threatening. You should submit postmarketing adverse experience reports to the 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.

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](http://www.fda.gov/medwatch/report/mmp.htm).

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

Compliance Risk Management and Surveillance (HFD-330), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Biological product deviations sent by courier or overnight mail should be addressed to Food and Drug Administration, CDER, Office of Compliance, Division of Compliance Risk Management and Surveillance, 10903 New Hampshire Avenue Bldg. 51, Room 4203 Silver Spring, MD 20993-0002.

### **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 125160/0**”.

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 April 16, 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 125160/0**”. 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.

### **PROMOTIONAL MATERIALS**

You may submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communication, 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.

FDA Form 2253 to the above address at the time of initial dissemination of the labeling or at the time of initial publication of the advertisement.

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.

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

Sincerely,

*Julie Beitz 4-22-08*

Julie Beitz, M.D.  
Director,  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research