CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125160/0

SUMMARY REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE

Food and Drug Administration

Summary Review for Regulatory Action

Date	April 21, 2008
From	Joyce Korvick Deputy Director Division of Gastroenterology Products Office of New Drugs III Center for Drug Evaluation and Research
Subject	Division Director Summary Review
BLA/Supplement #	BLA 125160/0
Applicant Name	UCB, Inc.
Date of Submission	April 30, 2007
Original BLA submission **Response to CR letter** **PDUFA Goal Date (second cycle)**	March 1, 2006 April 30, 2007 March 30 2008 (includes 3 month extension)
Proprietary Name / Established (USAN) Name	Cimzia (Certolizumab pegol)
Dosage Forms / Strength	Subcutaneous Injection: 200 mg lyophilized powder
Administration	400 mg subcutaneously initially and at Weeks 2 and 4. -- In patients who obtain a clinical response, the recommended maintenance regimen is 400 mg every four weeks
Proposed Indication(s)	Cimzia is indicated for reducing 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.
Action/Recommended Action:	**Approval with Medication Guide (Risk Evaluation and Mitigation Strategy) and Post-marketing Requirements**

1. Introduction

Crohn's disease, also known as regional enteritis, terminal ileitis, or granulomatous colitis, is an inflammatory bowel disease of unknown etiology. TNF-alpha is a key pro-inflammatory cytokine with a central role in the inflammatory processes. Excessive tumor necrosis factor alpha (TNFα) activity is believed to be involved in the pathogenesis of inflammatory bowel disease, including Crohn's disease.

Cimzia (Certolizumab pegol) is a tumor necrosis factor (TNF) blocker. Cimzia is a recombinant, humanized antibody Fab' fragment, with specificity for human tumor necrosis factor alpha (TNF-alpha), conjugated to an approximately 40kDa polyethylene glycol (PEG2MAL40K). Certolizumab pegol selectively neutralizes TNF-alpha.

Biological activities ascribed to TNF-alpha include the upregulation of cellular adhesion molecules and chemokines, upregulation of major histocompatibility complex (MHC) class I and class II molecules, and direct leukocyte activation. TNF-alpha stimulates the production of downstream inflammatory mediators, including interleukin-1, prostaglandins, platelet activating factor, and nitric oxide. Elevated levels of TNF-alpha have been implicated in the pathology of Crohn's disease. TNF-alpha is strongly expressed in the bowel wall in areas involved by Crohn's disease and fecal concentrations of TNF-alpha in patients with Crohn's disease have been shown to reflect clinical severity of the disease. Thus, there is clear biological plausibility to support use of TNF-alpha blockers in the treatment of patients with Crohn's disease.

There are currently 3 biologic products in this class approved for marketing in the U.S., and two are approved for use in Crohn's disease: Remicade® (Infliximab), Humira® (adalimumab). In addition, the biologic product, Tysabri® (Natalizumab), a humanized monoclonal antibody against the cellular adhesion molecule alpha 4-integrin, a new therapeutic class for treating Crohn's Disease was approved in January of 2008.

Remicade was initially given accelerated approval for Crohn's disease in August 1998; validation studies led to full approval in 2002. Humira, the other TNF-alpha blocker approved for Crohn's disease, received approval for that indication in February 2007. The third member of the TNF class is only approved for treatment of rheumatologic disease. In a study published in 2001, Enbrel (etanercept) did not show evidence of efficacy in Crohn's disease.

Biologic Product (route of administration)	**Labeled Indication**
Remicade (Infliximab) (intravenous)	1.) Reducing signs and symptoms and inducing and maintaining clinical remission in adult and pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy 2.) Reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease.
Humira (adalimumab) (subcutaneous)	1.) Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. 2.) HUMIRA is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.
Tysabri (natalizumab) (restricted access through the *CD TOUCH™ Prescribing Program)* (Intravenous)	Inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α. TYSABRI should not be used in combination with immunosuppressants.

The integrin receptor antagonist Tysabri, initially approved to treat MS, was approved for treating Crohn's disease in January 2008. Due to the risk of progressive multifocal leukoencephalopathy (PML), it is only available under a restricted distribution program, and the indication is restricted to patients who have failed therapies including TNF blockers, and who are not using concomitant immunosuppressive therapy.

Approved therapies for Crohn's disease include formulations of oral and IV steroids. Commonly used therapies also include 5-aminosalicylates (5-ASA's) and immunomodulators (azathioprine, 6-mercaptopurine, and methotrexate), but these are not approved in the U.S. for treating Crohn's disease. Use of any of the preceding has come to be considered part of "conventional therapy" for the disease.

2. Regulatory Background

This is the second review cycle for this biologic product.

BLA STN 125160 was originally submitted on February 28, 2006 and was granted a standard review. A complete response (CR) letter was issued on December 21, 2006. On April 30, 2007, the sponsor submitted a complete response for review. During the latter part of this review cycle, DGP requested and the sponsor submitted an updated review of safety. This submission resulted in a clock extension of three months. Additional time beyond the PDUFA goal date was needed to complete the safety review and successfully conclude discussions with the sponsor regarding labeling and post-marketing clinical trials.

The developmental history for Cimzia was complicated by the fact that it was initiated in 2003 and early communications and agreements were reached during the time the product was being reviewed in the Center for Biologic Evaluation and Research. There had been significant modifications of the program following the End-of-Phase 2 Meeting on April 15, 2003, between GD Searle (the IND holder at that time) and CBER. The CDER GI Division currently asks sponsors of Crohn's disease and ulcerative colitis products to provide replicated evidence of efficacy for induction and to provided maintenance studies lasting one year. The Reviewers in the initial cycle questioned, in particular, the adequacy of the evidence of efficacy for induction coming from a single controlled induction study.

After receiving the CR Letter, the applicant requested a meeting with the Division and OND management, which was held on May 30, 2007. It was established by FDA participants that the meetings and subsequent discussions and agreements with CBER about the Phase 3 studies designs were viewed by the CBER review Division at the time as having standing as End-of-Phase-2 agreements, and therefore CDER would view them the same way. Thus, the Phase 3 development program presented in the BLA should be viewed as complying with the designs that were agreed upon with the FDA.

Cimzia was approved for treating Crohn's disease in Switzerland in September 2007, but reportedly has not yet been distributed.

The EMEA published a negative opinion on Cimzia on 11/15/07, voicing concerns of insufficient evidence to show a benefit for induction, insufficient duration of the maintenance study, questions about product quality, and about bleeding events. In the EMEA's subsequent Refusal of Marketing Authorization on 3/20/08, the product quality and bleeding were removed as concerns, but the basis for refusing authorization was that there was insufficient evidence to show a benefit, due to only marginal effectiveness for induction that was too low to be relevant. In addition, the EMEA considered the study of maintenance to be too short.

- **Advisory Committee Meeting**
  This application was not referred to an FDA advisory committee because Cimzia is a member of the class of TNF blockers and the safety and efficacy data did not pose unique concerns beyond those applicable to other biologics approved for the treatment of Crohn's disease including other members of this class and Tysabri (natalizumab), an alpha-4 integrin blocker.

3. CMC

In the original CR letter (12/21/06) two product issues required additional responses:

- *"In your submission dated December 5, 2006, you proposed to submit a report in February 2007 to support the establishment of*
- *"Your submission dated December 1, 2006, described an amended comparabilty protocol to support PEG2MAL40K scale up to . However, it appears from Table 1 in this submission that , (validation campaign) used PEG2MAL40K manufactured at the scale. Since batches used the same process as your proposed commercial manufacturing process, there is no manufacturing change and thus no need for this comparability protocol. Therefore, please provide a statement for removal of the comparabilty protocol from the BLA. However, if there are differences between the manufacturing process used during the validation campaign and your proposed commercial manufacturing process, please highlight them in detail and submit a revised comparabilty protocol."*

The current submission responding to the FDA CR letter included an adequate response to these items. The product review team gave the following recommendation regarding this application:

"Cimzia is manufactured by a robust process with precautions for contamination . Cimzia is manufactured consistently, resulting in a safe and effective product. Two CMC issues raised in the original CR letter have been addressed and adequately resolved in this review."

I concur with the conclusions reached by the chemistry reviewers. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

The reviewers concluded the following:
"Certolizumab binds to human TNFα with high affinity and weakly cross-reacts with TNFα from non-human primates. However, Certolizumab does not recognize TNFα from rodents. So, toxicity studies with CERTOLIZUMAB were conducted in cynomolgus monkeys. In repeat dose toxicity studies in monkeys, slight hematological changes (decreased hemoglobin, RBC and packed cell volume, increased WBC) were observed and these changes were reversible. In addition, vacuolation of several tissues, particularly hemolymphoreticular tissues were observed in animals receiving high doses. This may be related to the pharmacological actions of the drug."

"Certolizumab was not genotoxic in a battery of genotoxicity assays. As Certolizumab does not cross-react with TNFα from rodents, reproductive toxicity studies (Segment I fertility and early embryonic development, Segment II teratogenicity and Segment III pre- and post- natal development) were conducted in rats using a anti-TNF antibody (cTN3 / cTN3 had no effects on the fertility and early embryonic development, it was not teratogenic and had no effects on pre- and post- natal development in rats." This evidence supports the pregnancy category B classification.

The FDA reviewers concluded that the applicant conducted adequate preclinical studies with Certolizumab to determine the safety of the drug, and the applicant's proposed dose appears to be safe for the proposed indication. Thus, from a preclinical standpoint, the BLA application is approvable.

No additional scientific pre-clinical data were submitted during the second review cycle. The pre-clinical team recommended specific changes to the labeling which were agreed upon by UBC, Inc.

I concur with the conclusions reached by the pharmacology/toxicology reviewers that there are no outstanding preclinical pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology reviewers concluded that Cimzia and the IV formulations of certolizumab pegol used in Phase 2 studies were comparable. The bioavailability for subcutaneous Cimzia is about 80% compared to IV formulations. Currently drug-drug interaction studies do not provide adequate evidence to include in the package insert, however the reviewers felt any interactions with methotrexate would be unlikely, because therapeutic biologics are not Cytochrome P450 substrates.

In the reviewer's population PK modeling, only weight and the presence of antibodies appeared to have any clinically significant impact on clearance. The presence of antibodies had more than a 30% effect on PK parameters. The reviewer recommended dose adjustment for antibody-positive patients.

The probability of developing antibodies appeared to be inversely related to Cimzia dose. The percentage of subjects with antibodies increased with continued dosing. The presence of antibodies effects the pharmacokinetics; from population PK analysis the clearance was estimated to increase by about four fold when antibodies were present, producing an estimated 86% reduction in trough levels and 72% reduction in AUC_τ.

In the initial review cycle, the Clinical Pharmacology reviewers did not believe that the applicant had fully explored the appropriate dose range and had not yet determined the proper dose for either induction or maintenance of remission. The reviewers recommended that the applicant redefine the dose-response relationship and use simulations based on current data for future clinical trial design to support product approval. The FDA's CR Letter of 12/21/06 included this one Clinical Pharmacology issue (see 12/21/06 CR Letter for specific wording of the deficiency).

In the current submission UCB, Inc. provided simulations based upon the original data finding that a change in Crohn's Disease Activity Index (CDAI) score correlated with certolizumab concentrations. The applicant argued that the use of higher doses leads to higher dropouts and is thus not increasing overall response rates for Crohn's disease. The reviewer noted [redacted] The reviewers still recommended that an increased dose or increased dosing frequency be investigated in future Crohn's disease trials.

For the current cycle, the reviewer found that the UCB, Inc. had provided an acceptable response to the FDA's CR Letter of 12/21/06. Recommendations regarding labeling were provided in the initial cycle Clinical Pharmacology review, and a few additional labeling recommendations were provided in this cycle.

[redacted]

At the end of the initial review cycle, there was an emerging issue regarding the reliability of laboratory testing done by [redacted] At the time of the action on 12/21/06 the extent of the problem was not clear. Subsequently, it was determined that the problem involved testing done at the [redacted] facility in [redacted] For the Cimzia development program, the impact is limited to the results of a PK drug interaction study with methotrexate. [redacted] should be omitted from the labeling.

Although the reviewer recommended that any future trials in Crohn's disease include exploration of increased dose or dose frequency, no Phase 4 Clinical Pharmacology requirements were recommended.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer regarding labeling. The review of efficacy with the currently proposed dosing regimen is commented on below in the Efficacy portion of my review. There are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

The product reviewers concluded that Cimzia is manufactured by a robust process with precautions for [redacted]

7. Clinical/Statistical-Efficacy

In this section I will describe the efficacy results, including the applicant's complete response, FDA analysis and the recommendation of the primary reviewers and the medical team leader.

The applicant's proposed indication changed during the conduct of the review as outlined below.

Cycle/Date Proposed	Proposed Indication
1st Cycle (3/01/06)	
1st Cycle (11/10/06)	
2nd Cycle (9/14/07)	
2nd Cycle Final	reducing 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.

In the original application, the sponsor submitted two double-blind, randomized, placebo-controlled trials in adult patients with moderate to severely active Crohn's disease defined by a Crohn's disease Activity Index (CDAI) score of 220 to 450 points. In both studies, clinical response was defined as > 100 point reduction from baseline in CDAI score; clinical remission was defined as a CDAI score < 150. According to the applicant both Study CDP870-031and Study CDP870-032 demonstrated a statistically significant, pre-specified, primary outcome.

Study CDP870-031 was a controlled trial of 6 months duration in 662 patients. There were two co-primary endpoints: clinical response at Week 6 following SC treatment at Weeks 0, 2, and 4, and clinical response at both Weeks 6 and 26. These endpoints were to be assessed in the patient stratum defined by a baseline C-reactive protein or CRP > 10 mg/L.

The results for Study CDP870-031 are provided below. At Week 6, the proportion of clinical responders was statistically significantly greater for Cimzia-treated patients compared to controls. The difference in clinical remission rates was not statistically significant at Week 6. The difference in the proportion of patients who were in clinical response at both Weeks 6 and 26 was also statistically significant, demonstrating maintenance of clinical response.

Study CDP870-031 – Clinical Response and Remission, Overall Study Population

Time point	% Response or Remission (95% CI)	
	Placebo (N = 328)	Cimzia 400 mg (N = 331)
Week 6		
Clinical Response#	27% (22%, 32%)	35% (30%, 40%)*
Clinical Remission#	17% (13%, 22%)	22% (17%, 26%)
Week 26		
Clinical Response	27% (22%, 31%)	37% (32%, 42%)*
Clinical Remission	18% (14%, 22%)	29% (25%, 34%)*
Both Weeks 6 & 26		
Clinical Response	16% (12%, 20%)	23% (18%, 28%)*
Clinical Remission	10% (7%, 13%)	14% (11%, 18%)

* p-value < 0.05 logistic regression test
# Clinical response is defined as decrease in CDAI of at least 100 points, and clinical remission is defined as CDAI ≤ 150 points

Study CDP870-032 was a randomized withdrawal study in which 428 patients who responded at Week 6 to open label Cimzia 400 mg administered SC at Weeks 0, 2, and 4 were randomized to either Cimzia or placebo administered every 4 weeks through Week 24. The primary endpoint was a comparison between the

treatment groups of the percentage of patients in clinical response at Week 26. This endpoint was to be assessed in the patient stratum defined by a baseline CRP > 10 mg/L.

The results for clinical response and remission are shown below. At Week 26, a statistically significantly greater proportion of Week 6 responders were in clinical response and in clinical remission in the Cimzia-treated group compared to the group treated with placebo.

Study CDP870-032 - Clinical Response and Clinical Remission

	% Response or Remission (95% CI)	
	Cimzia 400 mg x3 + Placebo N = 210	Cimzia 400 mg N = 215
Week 26		
Clinical Response[#]	36% (30%, 43%)	63% (56%, 69%)*
Clinical Remission[#]	29% (22%, 35%)	48% (41%, 55%)*

* $p < 0.05$
[#] Clinical response is defined as decrease in CDAI of at least 100 points, and clinical remission is defined as CDAI ≤ 150 points

Baseline use of immunosuppressants or corticosteroids had no impact on the clinical response to Cimzia.

Both the FDA clinical and statistical reviewers recommended a complete response be sent to the applicant based upon their review of these data at the end of the first review cycle. In study CDP870-031 the statisticians raised concerns about the disposition of selected patients which could impact the observed treatment differences, rendering the differences "not statistically significant". In exploratory analyses, FDA noted that the overall positive finding in Study CDP870-032 was driven primarily by responses in patient treated in countries other than the US. The significance of this finding is unclear. The clinical reviewer felt that Study 032 (maintenance) had a strong outcome. However, without sufficient evidence that Cimzia could be used to induce the response to be maintained, and without clinical experience maintaining the response achieved by any other approved therapy, he did not feel there was sufficient information to write adequate instructions for use. These concerns are presented below as they appear in the FDA CR letter (12/21/06) in which 4 clinical deficiencies are noted (#4-7):

4. Study CDP870-031 showed a small treatment effect that is not statistically robust when clinical response is assessed for the true intent-to-treat population (i.e., all patients randomized with a baseline CRP ≥10 mg/L) and patients with missing information are counted as non-responders. We do not view the ability to maintain a response once it has been achieved, as shown in Study CDP870-032, as substantial evidence of an ability to accomplish the task of inducing a response by reducing symptoms in patients who have active disease.

5. We are also not able to concur with the conclusion that Study CDP870-031 was a positive study for its primary objective, because we believe there was inadequate justification for excluding patient 525 from Site 22025 from the Week 6 results. Further, that patient appeared to have his baseline CRP results entered incorrectly in the database.

6. Study CDP870-032 showed that certolizumab pegol could maintain response in patients who have been previously induced into clinical response. However, in the absence of a finding that certolizumab pegol is able to induce a clinical response, a confirmatory study would be necessary to support your proposed maintenance indication.

7. We are concerned by the observation that Study CDP870-032 showed no significant effect of certolizumab pegol relative to placebo in the subgroup of US patients. Please conduct additional analyses to investigate possible explanations for this observation such as differences in patient characteristics, concomitant therapy practices, lots used, or other factors, that might explain the apparent differences between US and non-US sites.

The applicant's Complete Response to the FDA letter included no new clinical data, but addressed the issues raised in the letter. The applicant addressed issues 4-5 by supplying additional information regarding patient disposition and additional analyses. Several post-hoc, exploratory analyses were also performed by FDA reviewers. These analyses explored clinical response rates over the 26 week study period defined 1) as a decrease by 100 points in CDAI score, as per protocol and 2) as a decrease by 70 points in CDAI score (analogous to definitions of response for other approved products used to treat Crohn's disease). For these analyses, the FDA statistician used the intent-to-treat population defined as all patients randomized; subjects with missing data were considered to be non-responders. Using the protocol-defined response rate, treatment differences in the range of 3-11% were noted, which persisted from visit 2 to 26. When clinical response was defined as a decrease by 70 points, treatment differences of 4-14% were noted and persisted throughout the study period. Additional analyses explored the impact of higher vs. lower baseline CDAI scores. Treatment differences at Week 6 were somewhat larger for patients with baseline CDAI scores > 300 as compared to those with scores < 300 (15% vs. 3%). Although exploratory, these analyses support use of Cimzia in patients with more severe disease activity. These analyses are very well summarized in Medical Team Leader and Statistical Reviews. Summary tables of the FDA statistical exploratory analysis are provided for the reader below.

Week 4 Clinical Response Rates (≥ 70-Point Decrease in CDAI)

	Rate for Active Drug	Rate for Placebo	Difference	Odds Ratio	p
Remicade, 5 mg dose group	81%	17%	65%	22	<.001
Remicade all doses (5, 10, 20 mg)	65%	17%	48%	9.3	<.001
Humira, Study 1, labeled induction dose	58%	36%	22%	2.4	.007
Humira, Study 2	52%	34%	18%	2.1	<.001
Tysabri Confirmation Study (↑CRP)	51%	37%	15%	1.8	.001
Cimzia, ↑CRP Subgroup (1° Analysis)	50%	31%	19%	2.3	<.001
Cimzia, All Patients	44%	34%	10%	1.5	.011
Cimzia, Open Label, ↑CRP Subgroup (95%, C.I.)	83% (78%, 88%)				
Cimzia, Open Label, All Patients (95%, C.I.)	80% (76%, 84%)				

Week 4 Clinical Remission Rates (CDAI ≤ 150)

	Rate for Active Drug	Rate for Placebo	Difference	Odds Ratio	p
Remicade, 5 mg dose group	48%	4%	44%	21	<.001
Remicade, All doses (5, 10, 20 mg)	33%	4%	28%	11	.006
Humira Study 1, labeled induction dose	36%	12%	24%	4.0	.001
Humira Study 2	21%	7%	14%	3.5	<.001
Tysabri Confirmation Study (↑CRP)	24%	16%	8%	1.8	.009
Cimzia, ↑CRP Subgroup (1° Analysis)	20%	10%	10%	2.3	.018
Cimzia, All Patients	19%	11%	8%	1.9	.006
Cimzia, Open-Label, ↑CRP Subgroup (95% C.I.)	44% (37%, 51%)				
Cimzia, Open-Label, All Patients (95% C.I.)	43% (38%, 48%)				

By these analyses, at least for the pre-specified primary analysis group (elevated CRP), the effect size for clinical response in controlled studies of Cimzia is reasonably comparable to the effect sizes of Humira and

Tysabri. For remission, the effect of Cimzia appears weaker than that of the other TNF blockers but is like that of Tysabri.

Cimzia was used open label and without a control group in the induction phase leading into the maintenance phase of Study CDP870-032. The study was relatively large, and the confidence intervals around the rate estimates are fairly narrow. The rates, while uncontrolled, do appear to be appreciably greater than the historical placebo rates, even for the more recent Humira and Tysabri studies (the Remicade studies are much older). Although not adequately controlled to provide substantial evidence of efficacy, these results at least offer another estimate of effectiveness and provide some reassurance that a substantial proportion of patients would be expected to respond when Cimzia is used to treat active disease.

Upon review of the applicant's CR, the statistical reviewer agreed to accept the applicant's values for the p-values for the primary analysis from Study CDP870-031, but noted that the issue of lack of robustness remained because the results could be changed by reclassification of only one or two patients, and the results could be influenced by imputation technique.

The Clinical Reviewer for this cycle concurred with the Clinical Reviewer for the initial cycle in recommending against approval, citing that more statistically robust data in support of induction were warranted and that Cimzia should meet the standards of the other currently approved TNF blockers for Crohn's disease.

Upon consideration of all of the information submitted, and the regulatory agreements made during development the Medical Team Leader came to a different conclusion regarding the clinical efficacy of Cimzia. He "acknowledges the observations and concerns of the primary reviewers, but does not agree that the concerns compel the conclusion that Cimzia should not be approved". He further stated that "After review of the Applicant's Complete Response resubmission, the reviewers have concluded that the primary analysis of Study 031 can be accepted, and therefore it must be considered a positive study, albeit marginally so, and can be accepted as contributing toward substantial evidence of efficacy. Although the apparent inferiority of effectiveness compared to marketed products might be a consideration in an approval decision, it is not, in and of itself, adequate grounds to deny approval; the issue is whether the benefits and safety findings are within acceptable bounds, not whether they meet or exceed those of certain competitors. On further review of the clinical data, this reviewer finds there is adequate reason to expect the product to perform at least acceptably when used to treat active Crohn's disease, so that credible instructions for use can be written. Because the risk of this product is incurred primarily through its chronic use, and because there is strong evidence of its benefit in chronic use, the risk/benefit profile for Cimzia in Crohn's disease is similar to that of the marketed TNF blockers and is acceptable."

With regard to study CDP870-032 the Team Leader concluded "The randomized withdrawal maintenance study (Study 032) had a clinically significant and highly statistically significant result. Although it was one study of only of six month's duration, it is in accord with the 2003 agreements, and it is not unreasonable from a clinical standpoint to accept that study as contributing substantial evidence of efficacy in maintaining a clinical response. The anomalous finding of no difference between treatment arms in the subset of U.S. sites is not inconsistent with sampling variation, given the relatively small number of U.S. patients. Because the Applicant's analysis did not uncover reasons why the U.S. sites might be expected to have different outcomes, the study results can be viewed as supporting the application."

I agree with the Medical Team Leader's view of the data and find that these two studies support the currently proposed indication. Further, I agree that [redacted] not be used in this indication as recommended by the medical team. It should be noted that there is no strict regulatory definition for the [redacted]

8. Safety

The safety of Cimzia has been evaluated in a total of 4650 patients with Crohn's disease and other conditions. In controlled and uncontrolled studies, 1,564 subjects received Cimzia at some dose level, of whom 1,350 subjects received 400 mg Cimzia. Approximately 55% of subjects were female, 45% were male, and 94% were Caucasian. The majority of patients in the active group were between the ages of 18

and 64. The mean number of days patients have been exposed to 400 mg of Cimzia is 370 days, with 286 patients on drug for ≥ 24 months.

Review of the safety data included the original and current submission. In general the safety profile of Cimzia is similar to that of the other TNF-alpha blockers. Known serious risks with use of TNF blockers such as Cimzia include the occurrence of serious infections, including opportunistic infections, development of lymphoma and other malignancies, and development of demyelinating disorders and autoimmune disorders.

- **Clinical Trials Safety Database:**
  In controlled clinical studies of Crohn's disease, the incidence of infection (all severities) on Cimzia treatment was higher compared to placebo treatment (38% vs. 30%). The most common infections were upper respiratory tract infections. Serious infections occurred in 3% of Cimzia-treated patients as compared to 1% of patients on placebo treatment. The most common serious infections on Cimzia included bacterial and viral infections, pneumonia, and pyelonephritis.

  In completed and ongoing clinical studies that include over 4,650 patients, the overall rate of tuberculosis is approximately 0.5 per 100 patient-years. The rate in Crohn's disease studies was 0.3 cases per 100 patient-years. The reports include cases of pulmonary and disseminated tuberculosis. Cases of opportunistic infection have also been reported in clinical trials. Some cases of opportunistic infections and tuberculosis have been fatal

  Malignancies were reported at a similar rate in Cimzia- and placebo-treated patients in controlled trials, however, for some TNF blockers, more cases of malignancy have been observed among patients receiving those TNF blockers compared to control patients. In controlled studies of Cimzia for Crohn's disease and other investigational uses, there was one case of lymphoma among 2,657 Cimzia-treated patients and one case of Hodgkin lymphoma among 1,319 placebo-treated patients. During controlled and open-labeled portions of Cimzia studies of Crohn's disease and other investigational uses, malignancies (excluding non-melanoma skin cancer) were observed at a rate (95% confidence interval) of 0.6 (0.4, 0.8) per 100 patient-years among 4,650 Cimzia-treated patients versus a rate of 0.6 (0.2, 1.7) per 100 patient-years among 1,319 placebo-treated patients. The size of the control group and limited duration of the controlled portions of the studies precludes the ability to draw firm conclusions.

  Rates in clinical studies for Cimzia cannot be compared to the rates of clinical trials of other TNF blockers and may not predict the rates observed when Cimzia is used in a broader patient population. Patients with Crohn's disease or other diseases that require chronic exposure to immunosuppressant therapies may be at higher risk than the general population for the development of lymphoma, even in the absence of TNF blocker therapy. The potential role of TNF blocker therapy in the development of malignancies is not known.

  Autoantibodies developed in 4% of Cimzia-treated and in 2% of placebo-treated patients. One Cimzia-treated patient developed symptoms of a lupus-like syndrome. No data are available on the response to vaccinations or the secondary transmission of infection by live vaccines in patients receiving Cimzia

  Rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease have been observed with Cimzia treatment.

  Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., leukopenia, pancytopenia, thrombocytopenia) have been infrequently reported with Cimzia.

  Serious infections were seen in clinical studies with concurrent use of anakinra (an interleukin-1 antagonist) and another TNF blocker, with no added benefit. Because of the nature of the adverse reactions seen with this combination therapy, similar toxicities may also result from combination of

anakinra and other TNF blockers. Therefore, the combination of Cimzia and anakinra is not recommended.

In response to the EMEA's citing of concerns about bleeding events in the negative opinion on 11/15/07, bleeding events were carefully reviewed by the clinical reviewer. A small number of serious bleeding events were identified; however, the severity of the events and the evidence of relationship to treatment did not appear to warrant a warning, but the reviewer recommended they should be reported as adverse events in the labeling.

Following the finding of abnormal coagulation testing in an Rheumatoid Arthritis Study in Europe, the Applicant identified that certolizumab pegol can produce artifactual elevations of aPTT for certain aPTT assay systems. On January 28, 2008, the Applicant submitted documentation regarding a commissioned study with researchers from the [redacted] This study was to investigate the possible interference of Cimzia, the Fab' fragment, and PEG in coagulation tests (including aPTT and PT assays). This additional study was performed after coagulation assays were performed in RA study CDP870-050 and results from the groups treated with Cimzia had more subjects with prolonged aPTT when compared to the placebo group, a three to four fold increase, and to a lesser extent prolonged PT. During the CD studies for certolizumab pegol coagulation testing (aPTT, PT, TT) were not performed during study visits. The clinical reviewer noted that coagulation tests were not done in Crohn's trials, and recommended that they be included in any future studies.

- **Postmarketing data:**
  Cimzia is not marketed in the US. It is approved in Switzerland, but has not be marketed. No post-marketing data has been submitted to this BLA.

  The Office of Surveillance and Epidemiology Divisions agreed with the recommended Medication Guide for the safe use of Cimzia. While it is recommended that Cimzia be prepared and administered by a health care professional, the Medication Guide will provide important information on the safety profile of Cimzia, of which the patient should be informed. The tradename was found acceptable. The Division of Gastroentrology worked closely with the Division of Epidemiology in OSE when developing the Post Marketing Requirements. Future development of final protocols will be made in consultation with that Division.

  The approval letter requests that UBC, Inc. 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.

- **Risk Evaluation and Mitigation Strategy (REMS) – Medication Guide:**
  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)(2)).

  The only elements of the REMS deemed necessary will be a Medication Guide and a timetable for submission of assessments of the REMS.

  In addition, 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.

9. Pediatrics

The PREA requirements for ages 0 to 5 yeas were waived because studies are impossible or highly impractical due to the small number of pediatric Crohn's disease patients less than 6 years of age. Pediatric studies for ages 6 to 17 years are deferred until additional data from post-marketing studies in adults have been submitted. The applicant also presented an outline of a program aimed at evaluating effectiveness, safety, and PK of Cimzia in the pediatric population. The proposal was presented to the Pediatric Review Committee (PeRC), which agreed with the partial waiver, but requested that the effectiveness evaluation The Applicant agreed to

10. Other Relevant Regulatory Issues

- **DSI Audits:** Acceptable except for
- **Compliance Audit:**
  At the end of the initial review cycle, there was an emerging issue regarding the reliability of laboratory testing done by At the time of the action on 12/21/06 the extent of the problem was not clear. Subsequently, it was determined that the problem involved testing done at the For the Cimzia development program, the impact is limited to the results of a PK drug interaction study with methotrexate.

  The phase 3 clinical trials had clinical laboratory work performed at

  which was not named in the FDA warning letter. Therefore the clinical laboratory data in the phase 3 studies is acceptable.
- **Financial Disclosure:** form submitted and acceptable.
- **SEALD:** consult was obtained and essential elements of the PLR rule were made to the label and some additional editorial changes.

  There are no other unresolved relevant regulatory issues

11. Labeling

- **Physician labeling:**
  The following recommendation is made by the Medical Team Leader. The indication statement should refer to and maintenance of response, but should avoid use ." The indication should be limited to those who do not response to conventional therapy, but does not need

  In addition he recommends that the labeling should include warnings and precautions substantially similar to those in recently approved products in the TNF blocker class, namely warnings for serious infections, TB, hepatitis B reactivation, malignancies, hypersensitivity reactions, neurologic reactions, hematologic reactions, use with anakinra, heart failure, autoimmunity, immunizations, and immunosuppression. The malignancy section should include general TNF class information but should also present rates from Cimzia experience. Information about the interference with some aPTT assays should appear in the drug interaction section. The warnings regarding serious infections and TB should also appear in a boxed warning.

  Cimzia is to be prepared and administered by a health care professional.

  I concur with this approach; it is reflected in the approved label.

- **Carton and immediate container labels:**

Recommendations were passed to UCB, Inc. which were incorporated in the currently agreed upon carton on container labels.

- **Patient labeling/Medication guide:**
  The medical team recommended a Medication Guide for safe use of Cimzia.
  I concur.

12. Decision/Action/Risk Benefit Assessment

- **Regulatory Action:** I recommend approval of this supplement with the agreed upon labeling changes. This is agreement with review team recommendations.

- **Risk Benefit Assessment:**
  Cimzia has clearly demonstrated efficacy in the maintenance of clinical remission using results of Study CDP870-032. The evidence provided from study CDP870-031 demonstrates statistically significant difference between placebo and Cimzia for response rates of the signs and symptoms of active Crohn's disease, though somewhat lower than for the currently marketed TNF-alpha blockers and Tysabri. However, when additional analyses are performed using the change in CDAI score of ≤ 70 points from baseline at 4 weeks, the rates for clinical response are comparable to Humira and Tysabri. Thus, based upon the totality of data the efficacy has been demonstrated for the proposed indication.

  The safety profile is comparable to other marketed TNF blockers.

  The risk/benefit profile is acceptable because the risk is largely determined by the risk of chronic use. Study CDP870-032 demonstrates, for patients who have a response at 6 weeks and go on to take Cimzia for maintenance, a clinically significant response is sustained at a meaningful level. Given these clinical data the risk/benefit for maintenance therapy with Cimzia is favorable.

- **Recommendation for Postmarketing Risk Management Activities:**
  Medication Guide and REMS assessment (see safety discussion)

- **Recommendation for other Postmarketing Requirements:**
  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 post-marketing 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.

  The following is the list of specific requirements outlined in the approval letter.

  1) "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 clinical trial 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.

  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..

  3) CDP870-033, an ongoing open-label trial to asses 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..

4) CDP870-034, an ongoing open-label trial to asses 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.

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..

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.

Material Reviewed/Consulted: OND Action Package	**Reviewer**
Medical Officer Review	I. Chen (4/15/08) S. Bezabeh (12/19/06)
Medical Team Leader Review	J. Hyde (4/18/08)
Statistical Review	M. Fan (4/15/08)
Pharmacology Toxicology Labeling Comments	S. Chakdar (XX)
Tertiary Pharmacology Review	P. Brown (4/18/08)
Office of Biologic Products Review	G. Gill-Sangha (9/26/08)
Clinical Pharmacology Review	T. Gosh (11/8/07)
OSE/Division of Risk Management Review	J. Best (4/1/08) – Med Guide S. Rawls (1/3/08) – Carton/Container Labels
OSE/Division of Epidemiology Review	S. Kaplan (1/8/08, 4/15/08)
OSE/Division of Medication Error Prevention Review	L.Holmes (8/24/08) L. Pincock (4/3/08)
SEALD Labeling Review	I. Masucci (1/9/08)

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
SEALD=Study Endpoints and Label Development Division

Other documents reviewed included the Team Leader Review Memo dated December 19, 2006, for the initial review cycle, as well as to the primary review documents from that cycle. This memorandum summarizes selected information from the review documents, with primary emphasis on the issues to be resolved in the current review cycle.