CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125160/0

OFFICE DIRECTOR MEMO

MEMORANDUM

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

DATE: April 22, 2008

FROM: Julie Beitz, MD

SUBJECT: Office Director Memo

TO: BLA STN 125160 Cimzia (certolizumab pegol); UCB, Inc.

Summary

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 recombinant, humanized antibody Fab' fragment which binds to and neutralizes human TNFα in a dose-dependent manner. The Fab' fragment is manufactured in *E. coli*, purified, and conjugated to polyethylene glycol which extends the terminal plasma elimination half-life to approximately 14 days. This memo documents my concurrence with the Division of Gastroenterology Product's recommendation for the approval of CIMZIA for reducing the signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.

Like other biologic products approved for Crohn's disease, the indicated population will be limited to patients with an inadequate response to conventional therapy, although CIMZIA clinical trials did not specifically limit enrollment to such patients. The known serious adverse effects associated with the use of these products would dictate that their use be reserved after conventional therapies have been tried.

The safety profile of CIMZIA is comparable to that of other TNF blockers approved for the treatment of Crohn's disease. Because the risks are incurred primarily as the result of chronic use, and there is clear evidence of efficacy with chronic use, the risk / benefit profile of CIMZIA for use in Crohn's disease is acceptable.

Regulatory History

BLA STN 125160 was originally submitted on February 28, 2006 and was granted a standard review. A complete response 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 postmarketing clinical trials. Inspectional issues raised during the first review cycle have been addressed.

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.

Dosing

CIMZIA is supplied as a white lyophilized powder for reconstitution and subcutaneous (SC) injection. The recommended dose is 400 mg (given as two SC injections of 200 mg) initially and at Weeks 2 and 4.

Patients who obtain a clinical response may continue therapy with CIMZIA dosed at 400 mg every 4 weeks.

Efficacy

The efficacy of CIMZIA was assessed in two double-blind, randomized, placebo-controlled trials in adult patients with Crohn's disease defined by a Crohn's disease Activity Index (CDAI) score of 220 to 450 points. 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 $\geq$ 10 mg/L. 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 proportion of patients in clinical response at Week 26. This endpoint was to be assessed in the patient stratum defined by a baseline CRP $\geq$ 10 mg/L. In both studies, clinical response was defined as $\geq$ 100 point reduction from baseline in CDAI score; clinical remission was defined as a CDAI score $\leq$ 150.

In the original BLA submission, the sponsor's analysis of Study CDP870-031 found the co-primary endpoints to be statistically significantly higher for CIMZIA 400 mg compared to placebo treatment. At Week 6, clinical responses were noted in 35% of CIMZIA-treated patients vs. 27% of placebo-treated patients. Clinical responses in patients at both Weeks 6 and 26 were noted in 23% of CIMZIA-treated patients vs. 16% of placebo-treated patients. Similar response rates were noted for the subset of patients with a baseline CRP $\geq$ 10 mg/L as compared to the overall population. For this analysis, the sponsor defined the intent-to-treat population as the number of patients randomized who received at least one dose of study medication and had one efficacy assessment. The FDA statisticians raised concerns about the disposition of selected patients which could impact the observed treatment differences.

In the complete response submission, the sponsor provided the patient disposition and clinical response information that had been requested by FDA. Several post-hoc, exploratory analyses were also performed by the 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, or 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 definition of 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. At Week 4, clinical response rates in patients with CRP $\geq$ 10 mg/L receiving CIMZIA were comparable to those previously observed with Tysabri and Humira.

Additional FDA analyses explored the impact of higher vs. lower baseline CDAI scores. Treatment differences at Week 6 were somewhat greater for patients with baseline CDAI scores > 300 as compared to those with scores $\leq$ 300 (15% vs. 3%). Although exploratory, these analyses support use of CIMZIA in patients with more severe disease activity.

With regard to the secondary endpoint of clinical remission, a larger proportion of CIMZIA-treated patients achieved a clinical remission compared to placebo-treated patients at Week 6, or at Week 6 and 26, but the differences between patient groups were not statistically significant.

For Study CDP870-032, the clinical response rate to therapy with open label CIMZIA 400 mg SC was 64%, much higher than that observed at Week 6 in Study CDP870-031. The sponsor's analysis found that among patients with a baseline CRP $\geq$ 10 mg/L who had responded to CIMZIA and who were then randomized at Week 6 to receive additional treatment with CIMZIA, the percentage of patients with clinical responses at Week 26 was 63%. Among such patients randomized to placebo treatment at Week 6, the response rate at Week 26 was only 36% ($p < 0.001$). In exploratory analyses, FDA noted that the

overall positive finding in this study was driven primarily by responses in patients treated in countries other than the US. The significance of this finding is unclear.

Regarding secondary endpoints, clinical remission rates at Week 26 were significantly higher in patients with a baseline CRP $\geq$ 10 mg/L randomized to receive maintenance therapy with CIMZIA compared to placebo treatment (48% vs. 29%).

Safety

The safety of CIMZIA has been evaluated in a total of 4650 patients with Crohn's disease and other conditions. 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.

The overall rate of tuberculosis in completed and ongoing trials of CIMZIA is approximately 0.5 per 100 patient-years. The rate in Crohn's disease studies is 0.3 per 100 patient-years. There have been reports of pulmonary and disseminated tuberculosis, as well as reports of opportunistic infections, some of which have been fatal. As with other TNF blockers, the product label for CIMZIA will have a boxed warning regarding the risk of serious infection, and discuss the risk of Hepatitis B virus reactivation in the WARNINGS AND PRECAUTIONS section.

In studies of Crohn's disease, malignancies were reported at a similar rate in CIMZIA- and placebo-treated patients. There was one case of lymphoma reported among CIMZIA-treated patients and one case of Hodgkin's lymphoma among placebo-treated patients.

Treatment with CIMZIA may result in the formation of auto-antibodies and, rarely, in the development 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.

Rat studies using a homologous anti-TNF antibody revealed no effects on fertility or early embryonic development, no evidence for teratogenicity, and no effects on pre-natal or post-natal development. CIMZIA will be labeled as Pregnancy Category B.

Certolizumab pegol was not found to be genotoxic in the Ames test, the human peripheral blood lymphocyte chromosomal aberration test, or the mouse bone marrow micronucleus assay. No long-term animal carcinogenicity studies have been conducted.

Pharmacokinetic Considerations

The pharmacokinetics of CIMZIA were evaluated in a cross-study population pharmacokinetic analysis of data from 1580 subjects, of whom 1268 were patients with Crohn's disease. This analysis found that age, gender, creatinine clearance, and white blood cell count did not influence the pharmacokinetics of CIMZIA. Anti-certolizumab pegol antibodies, repeated administration, weight, and immunosuppressant use were covariates that had a statistically significant effect on the pharmacokinetics of CIMZIA. None of the subject-dependent covariates had an effect that would require dose adjustment.

Tradename Review

The tradename "CIMZIA" is acceptable.

Labeling

Product labeling will include a Medication Guide as provided for under 21 CFR Part 208.

Postmarketing Requirements under PREA

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.

The deferred pediatric study required under section 505B(a) of the Federal Food, Drug and Cosmetic Act (FDCA) is considered a postmarketing requirement and is listed below:

1. Conduct a clinical trial 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.

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 the sponsor is required 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.

In addition, we have determined that only a clinical trial 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, the sponsor is required to revise the protocols for the following three clinical trials to extend the period of patient follow-up from the start of treatment, as follows:

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.

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 the sponsor is 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.

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)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug
(F) Whether the drug is a new molecular entity.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary to ensure that the benefits of CIMZIA outweigh its risks. In reaching this determination, we considered the following:

A. While it is not possible to estimate the size of the population likely to use CIMZIA, the number of patients affected with Crohn's disease in the United States is approximately 500,000.

B. CIMZIA will be approved to treat the signs and symptoms of and maintain clinical response in adult patients with moderately to severely active Crohn's disease, a serious medical condition. Complications of Crohn's disease can include intestinal obstruction, development of fissures,

abscesses and fistulas, malabsorption and malnutrition. These complications, when they arise, typically necessitate inpatient hospitalization, and medical or surgical intervention.

C. CIMZIA has been shown to reduce the signs and symptoms of Crohn's disease and maintain clinical response in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. See previous discussion in this memo under Efficacy.

D. The expected duration of therapy with CIMZIA in patients who obtain a clinical response may be as long as six months or more.

E. Known serious risks associated 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. In controlled trials in Crohn's disease, serious infections occurred in 3% of CIMZIA-treated patients as compared to 1% of patients on placebo treatment. 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. 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. Rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease have been observed with CIMZIA treatment. See previous discussion in this memo under Safety.

F. The term new molecular entity (NME) is generally not used with respect to biologics. Nevertheless, we have considered the fact that this product is a member of the class of tumor necrosis factor (TNF)-blockers.

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.

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

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