



Notification of Product Approval

The Division of Division of Gastroenterology Products would like to inform you of a recent new drug approval or update to the labeling of an approved drug. See below for a summary of the drug's approved use and any significant safety issues. The full prescribing information for this drug is attached and will also be posted on the Center for Drug Evaluation and Research (CDER) internet web site under "Drug Information" (<http://www.fda.gov/cder/drug/default.htm>).

Donna Griebel, M.D.
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration

PRODUCT NAME: Cimzia (certolizumab pegol) for subcutaneous injection
APPROVAL DATE: April 22, 2008
SPONSOR: UCB Inc.

X **New Product**

Indication:

Cimzia is a tumor necrosis factor (TNF) blocker 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.

Efficacy summary:

The efficacy and safety of Cimzia were assessed in two double-blind, randomized, placebo-controlled studies in patients aged 18 years and older with moderately to severely active Crohn's disease, as defined by a Crohn's Disease Activity Index (CDAI¹) of 220 to 450 points, inclusive. Cimzia was administered subcutaneously at a dose of 400 mg in both studies. Stable concomitant medications for Crohn's disease were permitted.

Study CD1

Study CD1 was a randomized placebo-controlled study in 662 patients with active Crohn's disease. Cimzia or placebo was administered at Weeks 0, 2, and 4 and then every four weeks to Week 24. Assessments were done at Weeks 6 and 26. Clinical response was defined as at least a 100-point reduction in CDAI score compared to baseline, and clinical remission was defined as an absolute CDAI score of 150 points or lower.

The results for Study CD1 are provided in Table 1. 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.

Table 1 Study CD1 – Clinical Response and Remission, Overall Study Population

Timepoint	% 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 CD2

Study CD2 was a randomized treatment-withdrawal study in patients with active Crohn’s disease. All patients who entered the study were dosed initially with Cimzia 400 mg at Weeks 0, 2, and 4 and then assessed for clinical response at Week 6 (as defined by at least a 100-point reduction in CDAI score). At Week 6, a group of 428 clinical responders was randomized to receive either Cimzia 400 mg or placebo, every four weeks starting at Week 8, as maintenance therapy through Week 24. Non-responders at Week 6 were withdrawn from the study. Final evaluation was based on the CDAI score at Week 26. Patients who withdrew or who received rescue therapy were considered not to be in clinical response. Three randomized responders received no study injections, and were excluded from the ITT analysis.

The results for clinical response and remission are shown in Table 2. 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.

Table 2 Study CD2 - 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.

REFERENCES

1. Best WR, Beckett JM, Singleton JW, Kern F: Development of a Crohn's Disease Activity Index, National Cooperative Crohn's Disease Study. *Gastroenterology* 1976; 70(3): 439-444

Safety summary:

Adverse reactions associated with the use of Cimzia are consistent with that seen with other TNF blockers currently on the market. The most serious adverse reactions associated with use of Cimzia are serious infections and malignancies. There is a boxed warning on the risk of serious infections (including Tuberculosis) on the product label. The labeling also has warnings for hepatitis B reactivation, hypersensitivity reactions, neurologic reactions, hematologic reactions, use with anakinra, heart failure, autoimmunity, use with live vaccines, and immunosuppression. Cimzia may cause falsely elevated results with some aPTT assays.

During controlled clinical studies, the proportion of patients with serious adverse reactions was 10% for Cimzia and 9% for placebo. The most common adverse reactions (occurring in $\geq 5\%$ of Cimzia-treated patients, and with a higher incidence compared to placebo) in controlled clinical studies with Cimzia was upper respiratory infection (20% Cimzia, 13% placebo), urinary tract infection (7% Cimzia, 6% placebo), and arthralgia (6% Cimzia, 4% placebo).

The proportion of patients who discontinued treatment due to adverse reactions in the controlled clinical studies was 8% for Cimzia and 7% for placebo. The most common adverse reactions leading to the discontinuation of Cimzia (for at least 2 patients and with a higher incidence than placebo) were abdominal pain (0.4% Cimzia, 0.2% placebo), diarrhea (0.4% Cimzia, 0% placebo), and intestinal obstruction (0.4% Cimzia, 0% placebo).

Infections

The incidence of infections in controlled clinical studies was 38% for Cimzia-treated patients and 30% for placebo-treated patients. The infections consisted primarily of upper respiratory infection (20% Cimzia, 13% placebo). The incidence of serious infections during the controlled clinical studies was 3% for Cimzia-treated patients and 1% for placebo-treated patients. Serious infections observed included bacterial and viral infections, pneumonia, and pyelonephritis.

Tuberculosis and Opportunistic Infections

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

In clinical studies of CIMZIA, the overall incidence rate of malignancies was similar for CIMZIA-treated and control patients. For some TNF blockers, more cases of malignancies have been observed among patients receiving those TNF blockers compared to control patients.