Arthritis Advisory Committee

Food and Drug Administration
Center for Drug Evaluation and Research

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Holiday Inn Gaithersburg, 2 Montgomery Village Avenue, Gaithersburg, MD

BLA 99-1234, Remicade™ (infliximab) Centocor

Question #1: Size and Completeness of Database

A total of 340 patients received Remicade in the ATTRACT study. Radiographic data from pre and post-treatment X-ray films were unavailable in 55 (16%) of these patients. Ten patients were ultimately unevaluable for analyses of radiographic outcomes because of a history of prior foot surgery. Despite these study limitations, a number of analyses support the robustness of the data with regard to structural outcome measures.

Please comment on the size and completeness of the database submitted by the sponsor. Is the ATTRACT database of sufficient size and quality to allow a determination to be made about the benefits of Remicade on radiographic progression in this patient population?

Question #2: Interpretation of Structural Outcome Measures

Patients treated with Remicade had, on average, less progression of erosive disease one year after initiation of therapy than did patients treated with placebo. These differences were evident in both primary and secondary analyses, the latter including analyses of structural outcome data from joints of the hands alone, feet alone, on the number of erosions alone, etc. In addition, more patients treated with Remicade, especially those treated at higher doses, were observed to have no progression of structural damage when compared to those treated with placebo.

a) Please comment on the relevance of secondary analyses of components of the primary radiographic outcome measure (e.g., erosion scores, joint space narrowing scores, etc.) to clinical outcomes. Should future trials include plans for assessing these components individually?

b) Please comment on the clinical relevance of data generated by the sponsor on other measures of structural outcomes (e.g., delayed progression, no progression of disease, less structural damage, etc.) If licensed, what additional studies should be performed to better characterize these outcomes or to better assess their clinical relevance (e.g., more follow-up data, long-term correlations with functional outcomes, etc.)?

c) Do the data support the sponsor's claim that Remicade prevents or delays progression of structural damage in patients with rheumatoid arthritis? To what degree, if any, can these benefits be extrapolated to patients with earlier onset, less-severe, or DMARD-responsive disease, i.e., to patients not studied in this trial?

Question #3: Interpretation of Pharmacologic and Dosing Information

Treatment with 3mg/kg Remicade q 8 weeks, the currently licensed dose, resulted in a wide range of serum levels. Those patients observed to have low serum trough levels of Remicade were less likely to experience improvements in ACR measures than those who had high levels. More patients treated with Remicade given 10 mg/kg every 8 weeks experienced an ACR 20 response (59%) or ACR 70 response (25%) at week 54 than did those receiving the currently

licensed dose (42% and 11%, respectively). Similarly, more patients treated with the higher doses of Remicade had evidence of radiographic improvements and were observed to have consistently higher serum trough levels than those treated with the currently license dose. No data were submitted on patients re-treated with higher doses of Remicade after failing on lower doses.

a) **Please comment on the dose-effects observed with Remicade, including the association of low or absent serum levels with poor clinical outcomes in patients receiving the recommended dose. Are these data, coupled with the observed clinical and radiographic findings in patients treated with higher doses of Remicade therapy, sufficient to warrant a recommendation to initiate therapy with Remicade at doses higher than that currently indicated, despite potential safety concerns?**
b) **Should current labeling allow for a range of doses and/or intervals so physicians may vary the dose?**
c) **Should the sponsor conduct additional studies of the safety of Remicade when administered initially at higher doses? If so, what types of studies should be conducted?**
d) **Should additional studies be performed to characterize the safety and efficacy of patients who fail initial treatment with 3mg/kg of Remicade given every 8 weeks and then are treated with higher and/or more frequent doses of Remicade?**

Question #4: Interpretation of Clinical vs. Structural Outcomes

While patients who had no X-ray progression on Remicade were more likely to experience an ACR20 response than were patients with progression, some patients experienced no X-ray progression and no evidence of clinical response. The relationship between lack of X-ray progression on study and long term functional benefits, if any, is unknown.

Is there any basis to support a claim (or a belief?) that patients treated with Remicade who do not experience improvements in their ACR 20 but show improvements on radiographic findings (e.g. no X-ray progression) have benefited from therapy?