DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE **February 11, 2005**

Christopher Firriolo
Director, Marketing Compliance
Centocor, Inc.
200 Great Valley Parkway
Malvern, PA 19355-1307

Re: BLA # 103772
Remicade® (infliximab)
Rev # 041004037

Dear Mr. Firriolo:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a visual aid (1N04391) for Remicade® (infliximab) submitted by Centocor under cover of Form FDA 2253 that is in violation of section 502(a) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. 352(a). The visual aid is misleading because it contains unsubstantiated effectiveness claims and omits information on the risks associated with Remicade in the treatment of rheumatoid arthritis and, therefore, suggests Remicade is safer and more effective than has been demonstrated by substantial evidence or clinical experience.

Background

According to the FDA-approved product labeling (PI), "Remicade, in combination with methotrexate, is indicated for reducing the signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis."

Treatment with Remicade is associated with numerous risks. There is a black box warning on the risk of infections, a contraindication against the use of Remicade in patients with moderate to severe heart failure, and several other warnings, including information on the risks of hematologic events, hypersensitivity reactions (including reactions that required hospitalization), and neurologic events associated with use of Remicade. The PI also includes precautions on autoimmunity and malignancy.

Unsubstantiated Effectiveness Claims

The visual aid includes the following presentations:

- The graph on page 3 displays "Median change in total van der Heijde-modified Sharp score in patients with early RA," highlighting a -1.4 median change from baseline for the Remicade 3mg/kg q 8 weeks + MTX treatment group. The -1.4 median change is shown in a section of the graph which contains the prominent claim "IMPROVEMENT".

- The graph on page 4 displays "Median change in van der Heijde-modified Sharp bone erosion score in patients with early RA," accompanied by the claim, "1.6-point median reduction in van der Heijde-modified Sharp bone erosion scores over 2 years in patients with ≤3 years' disease duration." The -1.6 median change is shown in a section of the graph which contains the prominent claim "IMPROVEMENT".

These presentations are misleading because they suggest that Remicade can reverse or heal the disease process (as distinct from slowing progression) in patients with early RA, as evidenced through improved radiographic response and negative erosion scores. The use of the prominent claim "IMPROVEMENT" along the x-axis of both graphs adds to the overall impression that Remicade can reverse or heal the damage caused by rheumatoid arthritis. Although Remicade is indicated for "inhibiting the progression of structural damage… in patients with moderately to severely active rheumatoid arthritis" (emphasis added), FDA is not aware of substantial evidence or substantial clinical experience to support claims that Remicade can reverse or heal the damage caused by RA.

As stated in the footnotes and bullets on pages 3 and 4 of the visual aid, the claims are based on a retrospective subset analysis of patients with ≤ 3 years' disease duration in the ATTRACT trial. The ATTRACT study does not constitute substantial evidence for the claims made by these presentations. The patients in this retrospective analysis included just 12 patients treated with placebo + methotrexate and 10 patients treated with Remicade 3mg/kg + methotrexate every eight weeks. There is no indication that the small median changes from baseline on Remicade (1.4 and 1.6 points) are statistically significant or represent actual improvement. The inclusion of footnotes and bullets describing the study is insufficient to correct the misleading impression created by this presentation that Remicade can reverse or heal the disease process in patients with RA.

Omission of Risk Information

The sales aid fails to include risk information in each specific part as necessary to qualify the safety and effectiveness claims for Remicade. Specifically, the first six pages of the eight-page visual aid contain various benefit claims for Remicade, but no risk information. The benefit claims made include effectiveness claims such as, "More Complete Control," "Efficacy Across A Broad Range of Patients," and "Sustained inhibition of structural damage, regardless of disease duration," which are presented as large, colorful, and bolded headers. Additional effectiveness claims and benefits

are presented throughout the detail aid with colorful charts or graphs, bolded headers, bullet points, and a significant amount of white space. Four pages of the detail aid also include a footnote referring the reader to "Important Information on page 7." These first six pages of the sales aid omit important risk disclosures regarding the use of Remicade, including the black box warning on the risk of infections as well as the contraindication against the use of Remicade in patients with moderate to severe heart failure.

The seventh page of the detail aid summarizes some risk information from the PI, but this is not sufficient to ensure that the claims in each part of the sales aid are truthful and non-misleading. Furthermore, this information is presented in single-spaced paragraph format without headers or presentation elements to emphasize to the reader that it is important safety information.

Conclusion and Requested Action

The visual aid contains unsubstantiated efficacy claims and omits important risk information associated with Remicade, and, therefore, misbrands Remicade in violation of section 502(a) of the Act, 21 U.S.C. 352(a).

DDMAC requests that Centocor immediately cease the dissemination of promotional materials for Remicade that contain claims the same as or similar to those described above. Please submit a written response to this letter on or before February 28, 2005, describing your intent to comply with this request, listing all promotional materials for Remicade that contain claims the same as or similar to those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Room 8B-45, 5600 Fishers Lane, Rockville, Maryland 20857, facsimile at (301) 594-6771. In all future correspondence regarding this matter, please refer to review #041004037 in addition to the BLA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Remicade comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

Catherine B. Gray, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications