October 5, 2001

IMPORTANT DRUG WARNING

Dear Healthcare Professional:

Centocor would like to inform you of important safety information for REMICADE® (infliximab), a biological therapeutic product indicated for the treatment of rheumatoid arthritis and Crohn's disease. Tuberculosis, and other serious opportunistic infections including histoplasmosis, listeriosis, and pneumocystosis, have been reported in both the clinical research and post-marking surveillance settings. Some of these infections have been fatal. Accordingly, Centocor has added a Boxed Warning to the labeling for the product and the Warnings and Adverse Reactions sections of the product labeling were revised on August 8, 2001.

The Boxed Warning was added as a result of the occurrence of 84 cases of tuberculosis worldwide, during the period from August 24th, 1998, through June 30th, 2001. Many of the cases reported were disseminated or extrapulmonary at the time of clinical presentation. Of the 84 cases, fourteen were reported to have died, although the primary cause of death was not always reported as TB. Most cases of TB were diagnosed within seven months of the initiation of REMICADE therapy and most reported the use of concomitant immunosuppressive medications. An increased risk of infections associated with tumor necrosis factor (TNF) blockade, is consistent with the known effects of TNF on macrophage activation and granuloma formation. Thus far, approximately 170,000 patients have been treated worldwide with REMICADE.

Clinicians are advised to carefully review the revisions to the labeling (see *BOXED WARNING, WARNINGS, PRECAUTIONS,* and *ADVERSE REACTIONS* sections of the labeling), which are summarized below. A copy of the full prescribing information is also enclosed.

The Boxed *WARNING* now contains the following information:

Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation), invasive fungal infections, and other opportunistic infections, have been observed in patients receiving REMICADE. Some of these infections have been fatal (see *WARNINGS*).

Patients should be evaluated for latent tuberculosis infection with a tuberculin skin test.[1] Treatment of latent tuberculosis infection should be initiated prior to therapy with REMICADE.

Additionally, the following new warning has been added to the package insert:

CASES OF HISTOPLASMOSIS, LISTERIOSIS, PNEUMOCYSTOSIS AND TUBERCULOSIS, HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. FOR PATIENTS WHO HAVE RESIDED IN REGIONS WHERE HISTOPLASMOSIS IS ENDEMIC, THE BENEFITS AND RISKS OF REMICADE TREATMENT SHOULD BE CAREFULLY CONSIDERED BEFORE INITIATION OF REMICADE THERAPY.

Centocor will make available patient information that informs patients of the potential safety risks possibly associated with REMICADE® (infliximab).

Centocor is committed to ensuring that REMICADE is used safely and effectively and is working closely with healthcare professionals to communicate the most recent labeling change. Centocor is also working to educate all healthcare professionals on minimizing the risk of active tuberculosis infection by taking appropriate measures to screen and treat for latent TB infection.

Centocor is committed to providing you with the most current product information for REMICADE. You can assist us with monitoring the safety of REMICADE by reporting adverse events to Centocor at 1-800-457-6399. Alternatively, this information may be reported to FDA's MedWatch reporting system by phone (1-800-FDA-1088), facsimile (1-800-FDA-0178), the MedWatch website at www.fda.gov/medwatch, or mailed to MedWatch, HF-2, 5600 Fishers Lane, Rockville, MD 20852-9787. Both healthcare professionals and consumers should use Form 3500 for reporting adverse events.

Should you have any questions or require further information regarding the use of REMICADE, please contact Centocor's Medical Affairs Department at 1-800-457-6399.

Sincerely,

Thomas F. Schaible, PhD
Executive Director, Medical Affairs

[1] American Thoracic Society, Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med* 2000;161:S221-S247

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