



October 2004

## IMPORTANT DRUG WARNING

Dear Healthcare Professional:

Centocor, Inc., would like to inform you of important safety information concerning malignancies for REMICADE<sup>®</sup> (infliximab), a biological therapeutic product indicated for the treatment of rheumatoid arthritis and Crohn's disease.

The Food and Drug Administration (FDA) convened its Arthritis Advisory Committee in March 2003 to review and advise on safety data for marketed tumor necrosis factor (TNF) blockers, including REMICADE. A particular focus was placed on the incidence of neoplasia and lymphoma in patients receiving these agents. Safety data from controlled clinical trials and post-marketing experience were examined. As a result of this evaluation, a warning concerning malignancy has been added to the labeling for all therapeutic agents that block TNF.

Centocor, in consultation with the FDA, has added a Warning to the labeling for REMICADE as follows:

### **WARNINGS - Malignancies**

In the controlled portions of clinical trials of all the TNF $\alpha$ -blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients. During the controlled portions of REMICADE trials in patients with moderately to severely active rheumatoid arthritis and Crohn's disease, 1 patient developed lymphoma among 1389 REMICADE-treated patients versus 0 among 483 control patients (median duration of follow-up 1.1 years). In the controlled and open-label portions of these clinical trials of REMICADE, 3 patients developed lymphomas (1 patient with rheumatoid arthritis and 2 patients with Crohn's disease) among 2410 patients (median duration of follow-up 1.1 years). In rheumatoid arthritis patients, this is approximately 3-fold higher than expected in the general population. In the combined clinical trial population for rheumatoid arthritis and Crohn's disease, this is approximately 6-fold higher than expected in the general population. Rates in clinical trials for REMICADE cannot be compared to rates of clinical trials of other TNF blockers and may not predict rates observed in a broader patient population. Patients with Crohn's disease or rheumatoid arthritis, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma. The potential role of TNF $\alpha$ -blocking therapy in the development of malignancies is not known (see ADVERSE REACTIONS, Malignancies). No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving REMICADE; thus additional caution should be exercised in considering REMICADE treatment of these patients.

Also, the Adverse Reaction section of the REMICADE® (infliximab) prescribing information has been updated to add the following section on malignancies.

#### **ADVERSE REACTIONS – Malignancies**

Among 2410 patients with moderately to severely active rheumatoid arthritis and Crohn's disease treated with REMICADE in clinical trials with a median of 1.1 years of follow-up, 3 patients developed lymphomas, for a rate of 0.07 cases per 100 patient-years of follow-up in patients with rheumatoid arthritis and 0.12 cases per 100 patient-years of follow up in the combined clinical trial data for rheumatoid arthritis and Crohn's disease patients. This is approximately 3-fold higher in the RA clinical trial population and 6-fold higher in the overall clinical trial population than expected in an age-, gender-, and race-matched general population based on the Surveillance, Epidemiology and End Results Database. Rates in clinical trials for REMICADE cannot be compared to rates of clinical trials of other TNF blockers and may not predict rates observed in a broader patient population. An increased rate of lymphoma up to several fold has been reported in the Crohn's disease and rheumatoid arthritis patient populations, and may be further increased in patients with more severe disease activity. Other than lymphoma, 13 patients developed malignancies, which was similar in number to what would be expected in the general population. Of these, the most common malignancies were breast, colorectal, and melanoma. (See WARNINGS, Malignancies.)

Malignancies, including non-Hodgkin's lymphoma and Hodgkin's disease, have also been reported in patients receiving REMICADE during post-approval use.

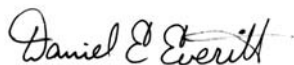
Since August 24, 1998, when REMICADE was approved in the United States, approximately 576,000 patients have been treated with REMICADE worldwide.

Enclosed please find the updated prescribing information as well as the patient information sheet.

Centocor is committed to ensuring that REMICADE is used safely and effectively and 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](http://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,



Daniel E. Everitt, M.D.  
Vice President,  
Clinical Pharmacology and Global Pharmacovigilance  
Centocor, Inc.  
enclosure