December 2004

# IMPORTANT DRUG WARNING

Dear Healthcare Professional:

Centocor would like to inform you of important updates to the prescribing information for REMICADE® (infliximab), including the addition of a Warning on hepatotoxicity and an update to the existing Warning on Risk of Infections. REMICADE is a biological therapeutic product indicated for the treatment of rheumatoid arthritis, Crohn's disease and, most recently, ankylosing spondylitis.

In postmarketing experience worldwide, severe hepatic reactions including acute liver failure, jaundice/cholestasis, and hepatitis, including autoimmune hepatitis, have been rarely reported in patients receiving REMICADE. Since August 24, 1998, when REMICADE was approved in the US, approximately 576,000 patients have been treated with REMICADE worldwide. Approximately 3 patients in controlled clinical trials and 35 patients in the voluntary postmarketing reported events are considered to be severe hepatic reactions. A causal relationship between REMICADE and these events has not been established.

Centocor has added a Warning on Hepatotoxicity to the labeling for the product as follows:

**WARNINGS: Hepatotoxicity**

> Severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestasis, have been reported rarely in postmarketing data in patients receiving REMICADE. Autoimmune hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred between two weeks to more than a year after initiation of REMICADE; elevations in hepatic aminotransferase levels were not noted prior to discovery of the liver injury in many of these cases. Some of these cases were fatal or necessitated liver transplantation. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (e.g., ≥5 times the upper limit of normal) develops, REMICADE should be discontinued, and a thorough investigation of the abnormality should be undertaken. As with other immunosuppressive drugs, use of REMICADE has been associated with reactivation of hepatitis B in patients who are chronic carriers of this virus (i.e.,

surface antigen positive). Chronic carriers of hepatitis B should be appropriately evaluated and monitored prior to the initiation of and during treatment with REMICADE. In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving REMICADE without progression to severe hepatic injury (see ADVERSE REACTIONS, Hepatotoxicity).

The Adverse Reactions section and Patient Information Sheet were also updated to include important information regarding hepatotoxicity (see enclosed prescribing information).

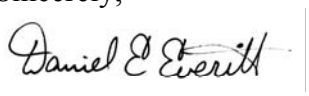
In addition, Centocor has added pneumonia to the existing Warnings on Risk of Infections based on clinical trial data in RA patients described in the Adverse Reactions section of the labeling.

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, 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,



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