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October 10, 2000

IMPORTANT DRUG WARNING

Dear Healthcare Professional:

We would like to bring to your attention recent post-marketing reports of adverse events in patients receiving ENBREL® (etanercept). Rare cases of central nervous system disorders, including demyelinating disorders such as multiple sclerosis, myelitis, and optic neuritis, have been reported in patients with rheumatoid arthritis who have received ENBREL therapy. Although the causal relationship to ENBREL therapy remains unclear, other tumor necrosis factor (TNF) antagonists administered to patients with multiple sclerosis have been associated with increases in disease activity[1,2]. Prescribers should exercise caution in considering the use of ENBREL in patients with preexisting or recent-onset central nervous system demyelinating disorders.

In addition, rare cases of pancytopenia, including aplastic anemia, some with a fatal outcome, have been reported in patients with rheumatoid arthritis who have received ENBREL therapy. Although the majority of patients who have developed pancytopenia on ENBREL therapy had recent or concurrent exposure to other anti-rheumatic medications known to be associated with myelosuppression (e.g., methotrexate, leflunomide, azathioprine, and cyclophosphamide), some patients had no recent or concurrent exposure to such therapies. Cases of pancytopenia occurred as early as 2 weeks after initiating ENBREL therapy. The causal relationship to ENBREL therapy remains unclear. Patients should be advised that if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on ENBREL, they should seek immediate medical attention. If significant hematologic abnormalities are identified, consideration should be given to discontinuation of ENBREL therapy.

As a result of these reports, the prescribing information for ENBREL (etanercept) has been revised to include the following new Warning statements.

WARNINGS

Neurologic Events

Rare cases of central nervous system demyelinating disorders have been described in spontaneous adverse event reports (see **ADVERSE REACTIONS**). The causal relationship to ENBREL therapy remains unclear. However, while no clinical trials have been performed evaluating ENBREL therapy in patients with multiple sclerosis, other TNF antagonists administered to patients with multiple sclerosis have been associated with increases in disease activity. Prescribers should exercise caution in considering the use of ENBREL in patients with preexisting or recent-onset central nervous system demyelinating disorders.

Hematologic Events

Rare reports of pancytopenia, including aplastic anemia, some with a fatal outcome, have been reported in patients with rheumatoid arthritis treated with ENBREL (see **ADVERSE REACTIONS**). The causal relationship to ENBREL therapy remains unclear. Although no high risk group has been identified, caution should be exercised in patients being treated with ENBREL who have a previous history of significant hematologic abnormalities. All patients should be advised that if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on ENBREL, they should seek immediate medical attention. If significant hematologic abnormalities are confirmed, consideration should be given to discontinuation of ENBREL therapy.

ENBREL is indicated for reducing signs and symptoms and delaying structural damage in patients with moderately to severely active rheumatoid arthritis. ENBREL is also indicated for reducing signs and symptoms of moderately to severely active polyarticular-course juvenile rheumatoid arthritis in patients who have an inadequate response to one or more DMARDs. ENBREL has been marketed in the U.S.A. since November 1998. Since market introduction, over 80,000 patients have received ENBREL therapy.

A revised package insert is enclosed. Should you have questions regarding the use of ENBREL, please call Immunex at 1 800-466-8639.

Healthcare professionals should report any serious adverse events possibly associated with the use of ENBREL to Immunex at 1 800-466-8639. Alternatively, this information may also be reported to FDA's MedWatch reporting system by phone (1 800-FDA-1088), Fax (1 800-FDA-0178), via the MedWatch website at www.fda.gov/medwatch, or by mail (using postage-paid form) to MedWatch, HF-2, 5600 Fishers Lane, Rockville, MD 20852-9787. Health professionals and consumers should use the Form 3500 for adverse event/product problem reporting.

Sincerely,

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Global Medical Affairs Department
Wyeth-Ayerst Laboratories

George Spencer-Green
Medical Director
Immunex Corporation

References: 1. Van Oosten BW, Barkhof F, Truyen L, et al. Increased MRI activity and immune activation in two multiple sclerosis patients treated with the monoclonal anti-tumor necrosis factor antibody CA2. *Neurology*. 47:1531-4, 1996. 2. Arnason BGW, et al. (Lenercept Multiple Sclerosis Study Group). TNF neutralization in MS: Results of a randomized, placebo-controlled multicenter study. *Neurology*. 53:457-65, 1999.

Enbrel is manufactured by Immunex Corporation, Seattle, WA 98101 and is marketed by Immunex Corporation and Wyeth-Ayerst Pharmaceuticals.