

**ENBREL<sup>®</sup>**  
**(etanercept)**

FDA Arthritis Advisory Committee

August 17, 2001

IMMUNEX CORPORATION

And

WYETH-AYERST LABORATORIES

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## 1.0 INTRODUCTION

This document is submitted to facilitate discussion regarding the safety of TNF antagonist therapies and focuses attention on actions and communications implemented as a result of ENBREL<sup>®</sup> safety observations. Given the limitations in current understanding of the natural history of rheumatoid arthritis (RA), the contributions of RA disease severity, and the interaction of these elements with TNF antagonist therapy, Immunex and Wyeth-Ayerst welcome the opportunity for review and comment from the panel.

ENBREL is a protein comprised of the extracellular domains of two TNF (tumor necrosis factor) receptors attached to a portion of an IgG immunoglobulin (Mohler 1993). ENBREL acts primarily to bind and neutralize TNF. The conformation and binding specificity of the human TNF receptor reflect evolutionary selection and may have distinct advantages over other TNF antagonists. ENBREL contains entirely human amino acid sequence and is therefore only rarely immunogenic. ENBREL also binds and inhibits a second proinflammatory cytokine, lymphotoxin- $\alpha$ . ENBREL does not bind complement and is not associated with complement-mediated cell lysis.

In November 1998, ENBREL was approved for reducing signs and symptoms in patients with moderately to severely active rheumatoid arthritis (RA) who had an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDS). Since that time, the indications for ENBREL have expanded to include polyarticular course juvenile rheumatoid arthritis (JRA) (May 1999) and inhibition of structural damage in patients with moderately to severely active RA, including those who have not previously failed prior DMARD therapy (June 2000).

Because ENBREL was the first TNF antagonist approved for the treatment of RA, and because RA is a chronic disease that requires continuous therapy, Immunex and Wyeth-

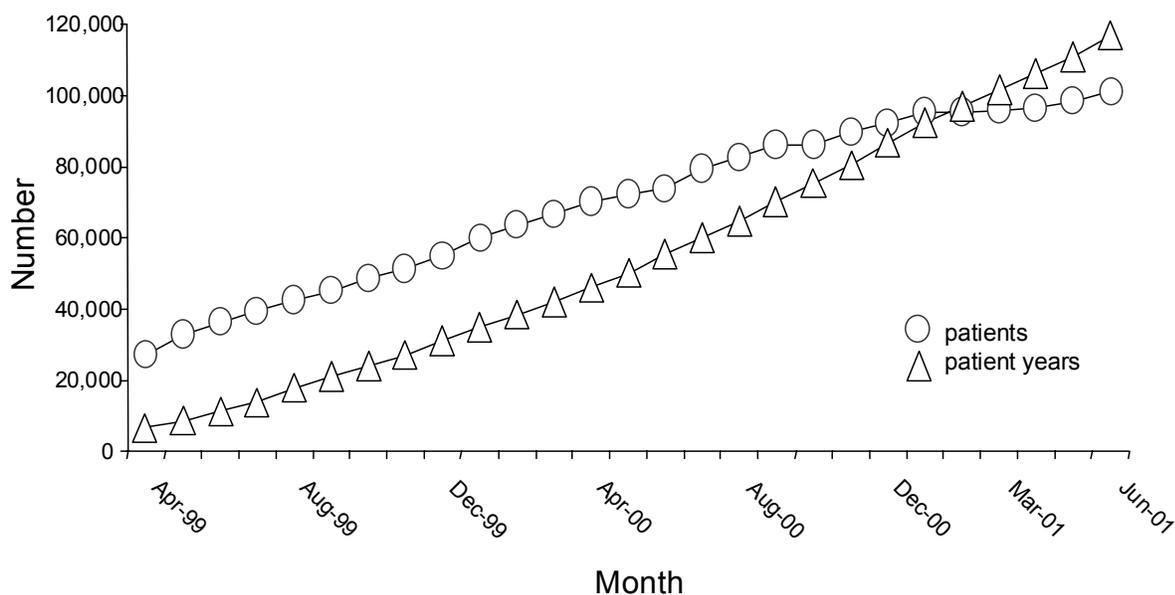
Ayerst have established a rigorous and comprehensive ENBREL pharmacovigilance program. This program includes retrospective and prospective studies for assessing the ENBREL safety profile over time. The ENBREL pharmacovigilance program integrates safety data from a variety of clinical trials, intensive post-marketing safety surveillance, and additional safety studies (see Section 6.0). Some of these trials were established in negotiation with regulators as part of post-approval commitments and some were initiated independently by Immunex and Wyeth-Ayerst. Safety information has been proactively collected, assessed, and communicated to physicians, patients, and regulators through label revisions, letters to healthcare providers, patient outreach, and scientific manuscripts and presentations. This document summarizes the key components of the ENBREL pharmacovigilance program and the actions taken to communicate safety information to both patients and the medical community.

## **2.0 ENBREL Experience**

Over 2000 patients have received ENBREL in RA clinical trials (both U.S. and Europe except where noted) comprising over 4342 patient-years of experience. In placebo-controlled RA trials, the proportion of patients who have discontinued therapy due to adverse events is approximately 4% in both ENBREL and placebo patients. In open-label extension studies, the safety profile of longer-term administration (up to 5 years) of ENBREL therapy remains stable over time.

Since ENBREL was approved in the United States (November 1998), the number of patients receiving commercial ENBREL therapy has steadily increased. This is illustrated in the following figure.

Post-Marketing Experience: Patient Number and Patient-Years of Exposure



As of July 2001, approximately 104,000 patients have been treated with ENBREL for over 120,000 patient-years of therapy. Approximately 78,000 patients in the United States and over 6,800 patient outside of the U.S. are now receiving commercial ENBREL therapy.

Despite the fact that ENBREL is now approved in the U.S. as an initial DMARD in RA, most ENBREL patients receiving commercial ENBREL therapy have long-standing RA and have had an inadequate response to prior DMARDs. Table 2.0A summarizes demographic and disease characteristics of patients with RA in ENBREL U.S. clinical trials, patients receiving commercial ENBREL therapy, and patients reporting post-marketing adverse events.

**Table 2.0A Comparison of Patient in U.S. RA Clinical Trials, Patients Receiving Commercial Therapy, and Patients in Post-Marketing Adverse Event Reports**

	Clinical RA Trials	Commercial*	Post-Marketing Adverse Event Reports†
Age (mean years)	50	55	56
Duration of Disease (mean years)	6.9	8.5	NA
% receiving corticosteroids	46	50	40

\* survey results

† patients who have had an adverse event reported in the post-marketing database

NA = not available

The patients studied in clinical trials have averaged over 50 years of age, with long-standing RA, and receiving concomitant corticosteroids. Patients in the “real world” setting are generally older and have a longer duration of disease.

### 3.0 Post-Marketing Safety Surveillance

#### 3.1 Spontaneous Adverse Event Reporting

Surveillance of spontaneously reported post-marketing adverse events plays a central role in evaluating the ENBREL safety profile and Immunex and Wyeth-Ayerst have established a comprehensive program to both capture and further characterize adverse events. In addition to compiling an adverse event database for safety surveillance and signal detection, Immunex performs extensive follow-up of reported events, including site visits where appropriate. Post-marketing surveillance also includes ongoing and systematic review of the medical literature.

### 3.2 Facilitated Adverse Event Reporting

Extensive communication between Immunex and ENBREL patients facilitates spontaneous adverse event reporting. Immunex has established three programs that facilitate direct contact with patients and their families. Every U.S. carton of ENBREL contains a toll-free telephone number that patients can use to contact Immunex representatives. The same number can be used to access the optional ENLIVEN program that provides educational information and support services for patients receiving ENBREL. Over 40,000 ENBREL patients currently participate in the ENLIVEN program, which includes a newsletter 8 times per year that displays the ENLIVEN telephone number and includes safety information. In addition, demand for ENBREL has led to an enrollment program to facilitate continued patient access to therapy, and every U.S. patient receiving ENBREL is enrolled in this program.

The patient service, ENLIVEN, and enrollment telephone programs collectively create a uniquely accessible relationship between Immunex and ENBREL patients. When health care providers, patients, or their families contact Immunex or Wyeth-Ayerst, those who mention any adverse experience are transferred to a registered nurse for further evaluation, education, and follow-up according to established protocols. For serious reports (including consumer-initiated reports), follow-up is pursued with the treating health care professional to verify diagnosis and outcome. Over 34,000 calls per month (December 2000 through April 2001) are processed through these programs. Call volumes correlate with the number of serious adverse events reported ( $R = 0.94$ ).

As a result of this facilitated reporting, Immunex receives a high volume of reports directly from patients in addition to the traditional flow of adverse events from health care providers. In fact, less than 22% of ENBREL adverse event reports originate from health care providers, with the remainder being initiated by patients. The high reporting volume increases the opportunity to identify signals of rare events.

### **3.3 Limitations of Spontaneous Adverse Event Reporting**

Post-marketing safety surveillance has limitations that are widely recognized. In general, the voluntary, retrospective, and anecdotal nature of the reporting, and the absence of a control group or a true denominator reduce reporting rates to incomplete estimates of event frequency. A number of factors affect the interpretation of post-marketing reports:

- Degree of underreporting
- Passive versus facilitated reporting
- Incompleteness of medical information
- Unverified diagnoses
- Duplicate reports
- Confounding by disease, disease severity, comorbidities, and concurrent medications
- Causality (attribution) uncertain

It is important to recognize that these confounding factors may not apply equally to all products, or even to agents within the same class. Comparisons of products based on spontaneous data should be made with caution. However, post-marketing surveillance remains an appropriate means for early identification of safety signals from rare events, off-label prescribing, and prescribing in the setting of concurrent medications and comorbidities.

### **4.0 Labeling History of ENBREL**

The original ENBREL package insert (PI) was issued in November 1998. The PI has been revised since then as expanded indications have been approved and as additional safety information has become available. The current ENBREL PI is included in Appendix A.

In review of reported adverse events, both case level attribution analysis and population level analysis was performed. Safety issues have been included in the ENBREL PI based on the potential clinical significance of adverse events in order to facilitate informed decision-making by prescribing physicians. The major safety-related revisions of the PI are summarized in the following table.

**Table 4.0A Major Revisions to the ENBREL Package Insert**

<b>Date</b>	<b>Major Change(s)</b>	<b>Comments</b>
May 1999 <sup>a</sup>	Described post-marketing reports of serious infections occurring in patients while on ENBREL	Advised physicians to use caution in prescribing ENBREL to patients with a history of recurring infection or underlying conditions that predispose to infection (e.g., diabetes, heart failure, history of active or chronic infections) and advised discontinuation of ENBREL in patients who develop serious infections.
May 1999	Expanded indication for JRA	Added safety information from clinical trials in pediatric patients
June 2000	Expanded indication for inhibition of structural damage in patients who had not previously failed a DMARD	Added safety information from clinical trials in patients with RA of shorter duration
August 2000 <sup>b</sup>	Added a new section to summarize events in the post-marketing database; added a section in Precautions entitled "Neurological Events" to describe rare cases of central nervous system demyelinating disorders; described very rare reports of aplastic anemia; appended more comprehensive language regarding types of infections; and described patients who have manifest rashes in conjunction with autoantibodies	Advised prescribers to perform a careful risk/benefit evaluation of ENBREL therapy in patients with pre-existing or recent onset central nervous system demyelinating disorders.
October 2000 <sup>b</sup>	Described rare post-marketing reports of aplastic anemia in a new section of warnings entitled "Hematological Events." Demyelinating disorders moved to warnings.	Advised caution in prescribing ENBREL to patients with a history of significant hematological abnormalities
January 2001	Expanded section on post-marketing safety reports; described rare cases of tuberculosis in patients receiving TNF antagonists; added post-marketing safety observations from patients with JRA, added intestinal perforation and cutaneous lupus-like conditions to section on postmarketing reports	This revision also clarified that many of the serious infections occurred in patients on concomitant immunosuppressive therapy

a) described in a letter to health care professionals dated May 11, 1999

b) described in a letter to health care professionals dated October 10, 2000

## **5.0 Specific Safety Issues**

### Infections

Post-marketing safety reports of serious infections from clinical practice have led to warnings in the prescribing information for all approved TNF antagonists. Thirty ENBREL post-marketing reports of serious infections through April 1999 resulted in the implementation of a May 1999 warning in the product labeling and a letter to health care professionals (Appendix C).

One large clinic-based prospective study (Singh 1999) and one population-based retrospective study (Doran 2000a) have systematically evaluated serious infections in RA patients. They have demonstrated that RA patients are at higher risk for such adverse events with 0.03-0.09 serious infections per patient-year. These reports indicate that the increased risk of serious infection (operationally defined as requiring hospitalization or parenteral antibiotics) in RA patients is correlated with the patient's degree of disability, the presence of concurrent medical problems (such as diabetes, lung disease, or cardiovascular disease) and the use of corticosteroids or other immunosuppressive medications, as outlined in Table 5.0A.

**Table 5.0A Risk Factors for Serious Infections in Modern RA Cohorts\***

Risk Factor	Risk Ratio	P Values
Disability	1.5-1.6	<0.008
Diabetes	1.7-2.5	<0.004
Cardiovascular Disease	1.5	<0.001
Pulmonary Disease	1.4-1.8	<0.007
Corticosteroids	2.1-3.8	<0.001
Other immunosuppressant	2.1	<0.022

\*Adapted from Singh 1999 and Doran 2000a

In RA clinical trials with ENBREL, the observed rate of serious infections (0.04 per patient-year) has not been higher in patients receiving ENBREL than in placebo or control patients (Moreland 1999; Bathon 2000). In addition, there has been no increase in serious infections in conjunction with longer duration of ENBREL therapy (Moreland 2001). Over 85% of RA patients who have had serious infections in ENBREL clinical trials have chosen to continue ENBREL therapy. The profiles of these patients are, for the most part, consistent with those described in the prior literature on risk factors for serious infections cited above.

The rate of post-marketing reports of serious infections through June 2001 is 0.007 per patient and 0.007 per patient-year. Analysis of serious infection reports from post-marketing safety surveillance indicates that such patients have had an average of four comorbidities, seven concurrent medications, and that 74 percent have been receiving concomitant corticosteroid therapy. Further analysis of these reports reveals that the average duration of ENBREL therapy prior to infection is highly variable (193 days  $\pm$  189 standard deviation). No opportunistic infections have been observed in RA clinical trials and very rare opportunistic infections (0.0003 per patient and 0.0003 per patient-year) have been noted in post-marketing safety surveillance.

In response to the questions raised following reports of serious infections observed in post-marketing safety surveillance, Immunex has worked with the FDA to design and initiate a

randomized, double-blind, 1000-patient trial (Protocol 16.0029, see Appendix E) to prospectively evaluate the rates of infections in RA patients with comorbidities (e.g., diabetes, chronic pulmonary disease) who will receive ENBREL or placebo therapy in addition to their background therapies (see Section 6.3). An interim review by a data safety monitoring board raised no safety issues.

### Tuberculosis

Tuberculosis (TB) has been the focus of recent scrutiny in evaluating the safety of TNF antagonists. Through December 2000, Immunex had received no reports of TB from ENBREL clinical trials and 6 reports from post-marketing safety surveillance. In January 2001, Immunex and Wyeth-Ayerst inserted language regarding potential TB risk in the product labeling. The incidence of TB in the U.S. general population is 6.4 per 100,000 patient years (Centers for Disease Control Surveillance Reports). The incidence of patients with RA and receiving corticosteroids is unknown. No cases of TB have occurred in RA clinical trials with ENBREL. As there has been no pre-screening in US and European RA trials with ENBREL, 19 patients with a prior history of clinical tuberculosis have been included and 7 patients with a positive tuberculin skin test (with average duration of ENBREL therapy now over 580 days). No cases of tuberculosis reactivation from these trials have been observed. The number of TB reports from post-marketing safety surveillance (reporting rate of 0.0001 per patient, 0.00009 cases per patient year) is similar to the incidence expected in an age- and sex-matched U.S. population estimate.

### Demyelination

In May 2000, rare post-marketing reports had been received of patients with nervous system conditions associated with demyelination. Based on this information, in conjunction with

findings from two studies (Arnason 1999; Von Oosten 1996) associating other TNF antagonist therapies with worsening of patients with pre-existing multiple sclerosis (MS), Immunex implemented language in the U.S. prescribing information (August 2000). Additional product label changes, patient package insert changes, and letter to health care professionals were implemented October 2000, at which time reports of 11 patients with demyelination had been received (see Table 4.0). Immunex and Wyeth-Ayerst also collaborated with investigators who described such cases from post-marketing reports in an abstract (Mohan 2000) and manuscript (submitted).

The incidence of multiple sclerosis in the general population is up to 0.00006 per patient-year (Noseworthy 2000), prevalence is 0.0006-0.0013 per patient (Anderson 1991), and relapses are expected every 12 to 18 months. The epidemiology of demyelinating disorders in RA patients is not known. One patient with RA in clinical trials has been diagnosed with MS. The reporting rates of new onset MS in ENBREL post-marketing reports is 0.00005 per patient and 0.00004 per patient-year. There have been additional rare reports of optic neuritis and myelitis. A panel of neurologists, rheumatologists, and epidemiologists with expertise in demyelinating disorders was convened in March 2001 to assist Immunex and Wyeth-Ayerst in further assessing and investigating this issue. The panel of neurologists assisted with classification of complex cases. They concluded that the medical community had been appropriately informed through the product label change and a letter to health care providers and recommended continued safety surveillance. To further clarify the expected numbers of demyelination cases in the RA population and in patients receiving ENBREL, two large safety studies have been initiated: a 10,000 patient prospective RA safety registry (RADIUS) and a large retrospective linked claims database analysis where 0.5 – 1.0% of 4.5 million enrollees have RA (see Section 6.3).

### Aplastic Anemia

In June of 2000, two post-marketing reports described patients receiving ENBREL therapy with subsequent aplastic anemia. Aplastic anemia was added to the U.S. product labeling in August 2000. In October 2000, a letter to healthcare professionals was issued (Appendix D) bringing attention to additional statements in the Warning section of the PI and advising prescribers to exercise caution when administering ENBREL to patients with hematological abnormalities. In addition, the patient package insert for ENBREL (Appendix B) was revised to instruct patients to contact their physician immediately in the event that they develop symptoms suggesting aplastic anemia. To date there have been a total of 4 reports of aplastic anemia. The current reporting rates are 0.00004 per patient and 0.00003 per patient-year. The relative risk of developing aplastic anemia in patients with RA has been reported to be increased 5.8- to 7.6-fold (Bamelou 1993; Kaufman 1991).

Wyeth-Ayerst and Immunex convened an expert panel of hematologists December 2000 to evaluate hematological events in patients who had received ENBREL therapy. The panel concluded that there was insufficient information to establish a causal relationship between ENBREL therapy and very rare reports of aplastic anemia and recommended continued safety surveillance.

### Cutaneous lupus-like conditions

By June 2000, there had been four post-marketing reports of patients manifesting rash in conjunction with autoantibodies while receiving ENBREL therapy. Language was appended to the product label describing such cases in August 2000. In January 2001, the Precautions section of the ENBREL PI was also revised to include rare reports of patients with rheumatoid factor positive RA who had tested positive for autoantibodies in conjunction with rashes compatible with cutaneous variants of lupus. None of these patients have met the

diagnostic criteria for systemic lupus erythematosus. No cases of lupus-like disorders have been observed in ENBREL RA clinical trials. No cases of patients developing lupus-like conditions or other new autoimmune diseases have been observed among 415 ENBREL patients in a 2-year controlled trial (Bathon, 2000) and 628 patients in an open-label extension trial (Moreland 2001) where investigators were specifically asked to record symptoms or findings indicative of new autoimmune disease.

### Malignancy

The initial package insert of November 1998 states: “The possibility exists for anti-TNF therapies, including ENBREL, to affect host defenses against infections and malignancies...”. Safety surveillance conducted since that time has led to no subsequent revisions in the product labeling. Early preclinical studies indicated that TNF was cytotoxic for certain tumor lines (Old 1985; Creasey 1986; Palladino 1987). However, there is increasing evidence that TNF is a growth factor for certain malignancies (Filella 1996; Brach 1992; Freedman 1992; Moore 1999; Warzocha 1998; Naylor 1993) and may enhance the metastatic potential of certain tumors (Malik 1990). Since the clinical implications of sustained TNF inhibition have not yet been determined, the ENBREL pharmacovigilance program includes careful long-term surveillance for malignancies.

Malignancy case reports from both clinical trials and post-marketing safety surveillance are analyzed at both the case level (where histologic types and stages of malignancies are characterized) and at the population level (assessing whether the observed numbers and types of malignancies are greater than expected in the treated population). The incidence of total malignancies in patients receiving ENBREL in clinical trials and extension studies (0.009 events per patient-year) has not been different than the incidence expected in the age- and sex-matched U.S. general population using the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) database (Kosary 1995). In the ENBREL post-

marketing safety surveillance program, there has been no indication of a cumulative increase in malignancies over time or that the number of observed malignancies exceeds the number expected from the SEER registry data. Further observation is required to establish whether chronic TNF antagonist therapy is associated with altered risk of malignancy.

It has been well established that RA patients are at increased risk for development of both non-Hodgkin's lymphoma and Hodgkin's disease (Isomaki 1978; Gridley 1993; Mellekjær 1996; Thomas 2000), particularly patients with high levels of disease activity (Baecklund 1998). The incidence of lymphomas in ENBREL-treated patients from both clinical trials and post-marketing reports are consistent with the rates observed in the aforementioned epidemiological studies of RA patients. In addition, the histologic subtypes of lymphomas observed in patients who have received ENBREL therapy are in a distribution consistent with that observed in prior studies of RA patients (Kamel 1999). Longer term follow-up is ongoing to characterize lymphoma risk in patients receiving ENBREL.

## **6.0 ENBREL Pharmacovigilance Program**

Establishing the comprehensive safety profile for a new medication requires integration of observations from multiple safety data collecting systems: clinical trials, extension trials, surveillance of post-marketing spontaneous (or facilitated) reports and literature, post-approval studies evaluating specific patient subpopulations, and assessments that provide insights on both the relative risk and incidence of adverse events from "real world" community-based prescribing experience. Interpretation of safety observations is further facilitated by studies that evaluate the contemporary natural history (patients not receiving ENBREL) of the treated disease (RA) and confounding variables in the patient population. Studies must also be designed to permit evaluation of potential adverse events of longer latency.

In the ENBREL pharmacovigilance program, the major post-marketing safety objectives are to:

- Understand the disease course of RA, including the expected rates of adverse events such as infections and malignancies, in patients receiving conventional DMARD and/or corticosteroid therapies compared to those receiving ENBREL
- Determine the relative risk and incidence of adverse events, as power considerations permit, by conducting prospective and retrospective population-based studies in large and diverse patient populations
- Assess potential adverse events of long latency by performing studies with long-term follow-up
- Assess potential risks to special patient subpopulations, including children, geriatric patients, and those with comorbidities

## **6.1 Retrospective Post-Marketing Safety Surveillance Initiatives**

### Post-Marketing Reports

ENBREL post-marketing spontaneous (and facilitated) reports and literature reports will continue to provide ongoing information for hypothesis generation and signal detection. Although retrospective, anecdotal, and frequently inconclusive for establishing rates or causality, the post-marketing reports remain an important component of ongoing safety surveillance, and provides insights into off-label prescribing and into the impact of ENBREL in patients with multiple comorbidities and medications. They can also yield potential insights into rare safety issues or events potentially associated with long latency. Immunex and Wyeth-Ayerst believe that post-marketing safety surveillance provides an important window on the "real world" patient and prescriber experience with ENBREL therapy.

### Evaluation of Infections in a Population-Based RA Cohort

In 1998, Immunex commissioned a retrospective and population-based study of the epidemiology and natural history of serious infections in RA patients using the Olmsted County database in collaboration with Drs. Sherine Gabriel and Michele Doran. An interim analysis of this cohort observed over 30 years (6530 patient-years) has been presented (Doran 2000a; Doran 2000b) and a final report is in preparation. This work provides a useful benchmark perspective regarding the incidence of serious infections in RA patients and establishes risk factors associated with serious infections in the RA population.

### Linked Database Analysis of the Incidence of Adverse Events in RA patients

Immunex and Wyeth-Ayerst are initiating a collaboration with a large retrospective linked pharmacy and claims database to assess both the relative risk and incidence of selected adverse events such as demyelination and malignancies. This population-based study will capture a large U.S. RA claims database cohort, where chart validation is possible to verify observations. The incidence of adverse events for patients with RA will be compared among patients receiving ENBREL and other DMARDs.

## **6.2 Prospective Post-Approval Studies**

In cooperation with the U.S. Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products, a significant number of prospective safety studies have been designed and are enrolling patients as outlined in Table 4.0. A brief description of the study design for each trial is included in Appendix E. In addition, Immunex and Wyeth-Ayerst have independently initiated a 10,000 patient RA registry (RADIUS). These trials effectively address the ENBREL safety profile in special subpopulations (RA patients receiving concomitant sulfasalazine, hydroxychloroquine, or parenteral gold, RA with

comorbidities, geriatric RA, JRA, JRA with methotrexate, systemic onset JRA) and add to the safety database for rare events and potential safety issues of longer latency.

**Table 6.2A Post-Approval Studies with ENBREL**

Protocol #	Title	Status	No. of Patients	Duration of Study	Comments
016.0018†	Open-label extension treatment for DMARD-refractory RA patients in previous trials (various)	Enrolled	639	≥ 5 years	Includes patients from initial licensing studies who have received ENBREL continuously for up to 5 years with serial safety and efficacy observations
016.0023†	Open-label extension treatment for early RA patients (from Protocol 016.0012)	Enrolled	469	≥ 5 years	Patients in this study have received ENBREL for up to 3 years with serial safety and efficacy observations
016.0026†	Registry of ENBREL for patients with JRA	Enrolling	600*	3 years	Safety, including effects on growth and development parameters, among those who receive ENBREL will be compared to a similar cohort of patients with polyarticular course or systemic JRA who are receiving methotrexate.
016.0028†	Double-blind, randomized study comparing ENBREL + MTX vs. MTX alone in children with JRA	Enrolling	100*	6 months blinded; 6 months open-label	This study will compare the combination of ENBREL and methotrexate to methotrexate alone with respect to efficacy and safety in the treatment of children with polyarticular course JRA whose disease is not well controlled on NSAID plus methotrexate. Patients may also be eligible for open-label registry (016.0026)
016.0029†	Double-blind, randomized, placebo-controlled study of ENBREL in RA patients with comorbid disorders	Enrolling	1,000*	16 weeks	Patients must have at least 1 documented comorbidity, including diabetes mellitus (at least 200 pts), pulmonary disease (e.g. asthma or COPD), pneumonia within previous year, history of recurrent bronchitis, sinusitis, or UTI. Study monitored by a data safety monitoring board.
016.0031†	Safety and efficacy study of ENBREL in children with systemic onset JRA	Enrolling	75*	≤ 13 months	Safety of ENBREL in pediatric patients with systemic onset JRA. Patients may be eligible for open-label registry (016.0026)
016.0034	RA DMARD intervention and utilization study (RADIUS 1)	Initiating	5,000*	≥ 2 years	Prospective, observational; RADIUS 1 is designed to systematically collect and document use patterns, effectiveness, and safety of DMARD treatments currently used in the management of RA
016.0035	RA DMARD intervention and utilization study (RADIUS 2)	Developing	5,000*	≥ 2 years	Prospective, observational; RADIUS 2 is designed to systematically collect and document use patterns, effectiveness, and safety profile of ENBREL in the management of RA in clinical practice. Will compare experience with ENBREL use in Radius 2 to experience with other DMARDs in RADIUS 1.
016.0620†	Three month open label safety trial of ENBREL plus hydroxychloroquine, sulfasalazine, or injectable gold in patients with RA	Enrolling	120*	3 months	Prospective study to evaluate the safety of ENBREL in combination with other DMARDs.

† post-approval commitment with the FDA

\* proposed number

**Table 6.2A Post-Approval Studies with ENBREL (continued)**

Protocol #	Title	Status	No. of Patients	Duration of Study	Comments
0881A1-301-EU‡	Open-label safety study of etanercept in patients with rheumatoid arthritis	Enrolled	549	Up to 4 years	Includes patients from initial European double-blind studies. Enrolled patients received ENBREL continuously for up to 3 years with serial safety and efficacy observations.
EU registry‡	European RA patient registry	Enrolling	2000*		Prospectively collects both safety and efficacy information with registries conducted in the United Kingdom, Sweden, and the Netherlands
0881A1-308-EU‡	A double-blind study evaluating the efficacy and safety of the combination of etanercept and methotrexate in comparison to etanercept and methotrexate alone in rheumatoid arthritis	Enrolled	686	12 months with double-blind extension	This study will compare the combination of ENBREL and methotrexate to ENBREL alone and methotrexate alone with respect to efficacy and safety in RA patients who have failed previous DMARD therapy. Radiographic progression of disease will be evaluated. Standard safety and efficacy assessments will be performed.
0881A1-309-EU‡	A 6-month, double-blind comparison of etanercept, sulphasalazine, and the combination of etanercept and sulphasalazine in patients with active rheumatoid arthritis receiving sulphasalazine	Enrolled	260	6 months with double-blind extension	This study will compare the combination of ENBREL and sulphasalazine to ENBREL alone and sulphasalazine alone with respect to efficacy and safety in RA patients who have failed previous DMARD therapy. Standard safety and efficacy assessments will be performed.

‡ post-approval commitment with the EMEA

\* proposed number

## 7.0 Communication and Education

In addition to establishing and tracking observations from the ENBREL pharmacovigilance program, Immunex and Wyeth-Ayerst are also committed to communicating safety information to patients and the medical community. ENBREL education and communication initiatives are summarized in the following table.

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**Table 7.0A Summary of ENBREL Safety Education and Communication Initiatives**

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- Multiple product label revisions (See Table 4.0A )
  - Corresponding changes in patient package inserts: August 2000, October 2000 and January 2001
  - Letters to Health Care Professionals: May 1999, October 2000
  - Ongoing ENLIVEN program patient education and outreach; periodic newsletter contains safety information
  - 1-888-4ENBREL telephone access for product information
  - Collaboration with ACR for “Hotline” announcements
  - Collaboration with investigators preparing publications concerning safety issues
  - Safety abstracts submitted to national meetings
  - RADIUS RA safety registry: opportunity for rheumatologists to share observations and analyze practice data with colleagues and investigators
- 

The above measures assist physicians in making informed prescribing decisions and in promoting physician capacity to individualize patient care.

Immunex and Wyeth-Ayerst acknowledge the significant challenges associated with risk communication to patients, families and health care professionals. The ENBREL patient package insert has been revised to inform patients of potential risks and to urge patients to report adverse experiences to their physicians. All ENBREL labeling, physician-

directed advertising, and direct-to-consumer advertising include warnings regarding potential safety issues.

## **8.0 ENBREL Risk Benefit Assessment**

ENBREL is a fully human protein of low immunogenicity. It is the only TNF antagonist that can be used either as monotherapy or in combination with methotrexate. Clinical trials have consistently demonstrated that, in the great majority of patients treated, ENBREL acts rapidly and remarkably effectively in reducing clinical signs and symptoms of RA, even in patients with long-standing disease who have inadequate responses to methotrexate and other DMARDs (Moreland 1997; Moreland 1999; Weinblatt 1999). ENBREL frequently permits durable reduction or discontinuation of corticosteroids (Moreland 2001) and methotrexate and thus may permit avoidance of adverse effects associated with other medications. Moreover, ENBREL has substantial benefit in inhibiting the underlying structural joint damage characteristic of RA, with greater impact on bone erosions than that observed with methotrexate (Bathon 2000). ENBREL is also effective in pediatric patients (Lovell 2000) and is the only TNF antagonist approved for use in children with JRA.

Since approval, there have been reports of adverse events, some serious, in patients who have received ENBREL therapy. The expected incidence of most of these events in the RA population is generally not known and the causal relationship between such events and ENBREL therapy in most cases has not been established. All therapies available for the treatment of RA are associated with significant potential toxicities. Immunex and Wyeth-Ayerst have established an extensive pharmacovigilance program to further characterize the clinical experience with ENBREL.

RA is a common and frequently severe disease that can affect people of all ages, including children. It may be associated with unacceptable discomfort, progressive disability, and increased mortality. It is widely recognized that ENBREL has been a substantial contribution in rheumatologists' ability to successfully manage patients with RA and JRA.

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# ENBREL® (etanercept)

## DESCRIPTION

ENBREL (etanercept) is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) tumor necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1. The Fc component of etanercept contains the C<sub>H</sub>2 domain, the C<sub>H</sub>3 domain and hinge region, but not the C<sub>H</sub>1 domain of IgG1. Etanercept is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system. It consists of 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons.

ENBREL is supplied as a sterile, white, preservative-free, lyophilized powder for parenteral administration after reconstitution with 1 mL of the supplied Sterile Bacteriostatic Water for Injection, USP (containing 0.9% benzyl alcohol). Following reconstitution, the solution of ENBREL is clear and colorless, with a pH of 7.4 ± 0.3. Each single-use vial of ENBREL contains 25 mg etanercept, 40 mg mannitol, 10 mg sucrose, and 1.2 mg tromethamine.

## CLINICAL PHARMACOLOGY

### General

Etanercept binds specifically to tumor necrosis factor (TNF) and blocks its interaction with cell surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. It plays an important role in the inflammatory processes of rheumatoid arthritis (RA), polyarticular-course juvenile rheumatoid arthritis (JRA), and the resulting joint pathology.<sup>1,2</sup> Elevated levels of TNF are found in the synovial fluid of RA patients.<sup>3</sup>

Two distinct receptors for TNF (TNFRs), a 55 kilodalton protein (p55) and a 75 kilodalton protein (p75), exist naturally as monomeric molecules on cell surfaces and in soluble forms.<sup>4</sup> Biological activity of TNF is dependent upon binding to either cell surface TNFR.

Etanercept is a dimeric soluble form of the p75 TNF receptor that can bind to two TNF molecules. It inhibits the activity of TNF in vitro and has been shown to affect several animal models of inflammation, including murine collagen-induced arthritis.<sup>5,6</sup> Etanercept inhibits binding of both TNF $\alpha$  and TNF $\beta$  (lymphotoxin alpha [LT $\alpha$ ]) to cell surface TNFRs, rendering TNF biologically inactive.<sup>6</sup> Cells expressing transmembrane TNF that bind ENBREL are not lysed in vitro in the presence or absence of complement.<sup>6</sup>

Etanercept can also modulate biological responses that are induced or regulated by TNF, including expression of adhesion molecules responsible for leukocyte migration (i.e., E-selectin and to a lesser extent intercellular adhesion molecule-1 [ICAM-1]), serum levels of cytokines (e.g., IL-6), and serum levels of matrix metalloproteinase-3 (MMP-3 or stromelysin).<sup>6</sup>

### Pharmacokinetics

After administration of 25 mg of ENBREL by a single subcutaneous (SC) injection to 25 patients with RA, a mean ± standard deviation half-life of 102 ± 30 hours was observed with a clearance of 160 ± 80 mL/hr. A maximum serum concentration (C<sub>max</sub>) of 1.1 ± 0.6 mcg/mL and time to C<sub>max</sub> of 69 ± 34 hours was observed in these patients following the single 25 mg dose. After 6 months of twice weekly 25 mg doses in these same RA patients, the mean C<sub>max</sub> was 2.4 ± 1.0 mcg/mL (N = 23). Patients exhibited a two- to seven-fold increase in peak serum concentrations and approximately four-fold increase in AUC<sub>0-72 hr</sub> (range 1 to 17 fold) with repeated dosing. Serum concentrations in patients with RA have not been measured for periods of dosing that exceed 6 months.

Pharmacokinetic parameters were not different between men and women and did not vary with age in adult patients. No formal pharmacokinetic studies have been conducted to examine the effects of renal or hepatic impairment on ENBREL disposition or potential interactions with methotrexate.

Patients with JRA (ages 4 to 17 years) were administered 0.4 mg/kg of ENBREL twice weekly for up to 18 weeks. The mean serum concentration after repeated SC dosing was 2.1 mcg/mL, with a range of 0.7 to 4.3 mcg/mL. Limited data suggests that the clearance of ENBREL is reduced slightly in children ages 4 to 8 years. The pharmacokinetics of ENBREL in children < 4 years of age have not been studied.

## CLINICAL STUDIES

### Adult Rheumatoid Arthritis

The safety and efficacy of ENBREL were assessed in three randomized, double-blind, controlled studies. Study I evaluated 234 patients with active RA who were ≥ 18 years old, had failed therapy with at least one but no more than four disease-modifying antirheumatic drugs (DMARDs; e.g., hydroxychloroquine, oral or injectable gold, methotrexate [MTX], azathioprine, D-penicillamine, sulfasalazine), and had ≥ 12 tender joints, ≥ 10 swollen joints, and either ESR ≥ 28 mm/hour, CRP > 2.0 mg/dL, or morning stiffness for ≥ 45 minutes. Doses of 10 mg or 25 mg ENBREL or placebo were administered SC twice a week for 6 consecutive months. Results from patients receiving 25 mg are presented below.

Study II evaluated 89 patients and had similar inclusion criteria to Study I except that subjects in Study II had additionally received MTX for at least 6 months with a stable dose (12.5 to 25 mg/wk) for at least 4 weeks and they had at least 6 tender or painful joints. Subjects in Study II received a dose of 25 mg ENBREL or placebo SC twice a week for 6 months in addition to their stable MTX dose.

Study III compared the efficacy of ENBREL to MTX in patients with active RA. This study evaluated 632 patients who were ≥ 18 years old with early (≤ 3 years disease duration) active RA; had never received treatment with MTX; and had ≥ 12 tender joints, ≥ 10 swollen joints, and either ESR ≥ 28 mm/hr, CRP > 2.0 mg/dL, or morning stiffness for ≥ 45 minutes. Doses of 10 mg or 25 mg ENBREL were administered SC twice a week for 12 consecutive months. Results from patients receiving 25 mg are presented below. MTX tablets (escalated from 7.5 mg/week to a maximum of 20 mg/week over the first 8 weeks of the trial) or placebo tablets were given once a week on the same day as the injection of placebo or ENBREL doses, respectively.

The results of all three trials were expressed in percentage of patients with improvement in RA using American College of Rheumatology (ACR) response criteria.<sup>7</sup>

**Clinical Response**

The percent of ENBREL-treated patients achieving ACR 20, 50, and 70 responses was consistent across all three trials. The results of the three trials are summarized in Table 1.

The time course for ACR 20 response rates for patients receiving placebo or 25 mg ENBREL in Studies I and II is summarized in Figure 1. The time course of responses to ENBREL in Study III was similar.

Among patients receiving ENBREL, the clinical responses generally appeared within 1 to 2 weeks after initiation of therapy and nearly always occurred by 3 months. A dose response was seen in Studies I and III: 25 mg ENBREL was more effective than 10 mg (10 mg was not evaluated in Study II). ENBREL was significantly better than placebo in all components of the ACR criteria as well as other measures of RA disease activity not included in the ACR response criteria, such as morning stiffness.

In Study III, approximately 10% of patients treated with ENBREL achieved a major clinical response, defined as maintenance of an ACR 70 response over a 6-month period.

The results of the components of the ACR response criteria for Study I are shown in Table 2. Findings were similar in Studies II and III for patients treated with ENBREL.

After discontinuation of ENBREL, symptoms of arthritis generally returned within a month. Reintroduction of treatment with ENBREL after discontinuations of up to 18 months resulted in the same magnitudes of response as patients who received ENBREL without interruption of therapy based on results of open-label studies. Continued durable responses have been seen for up to 36 months in open-label extension treatment trials when patients received ENBREL without interruption.

A Health Assessment Questionnaire (HAQ),<sup>8</sup> which included disability, vitality, mental health, general health status, and arthritis-associated health status subdomains, was administered every 3 months during Studies I and III. All subdomains of the HAQ were improved in patients treated with ENBREL.

In Study III, health outcome measures were assessed by the SF-36 questionnaire. The eight subscales of the SF-36 were combined into two summary scales, the physical component summary (PCS) and the mental component summary (MCS).<sup>9</sup> At 12 months, patients treated with 25 mg ENBREL showed significantly more improvement in the PCS compared to the 10 mg ENBREL group, but not in the MCS.

**Radiographic Response**

In Study III, structural joint damage was assessed radiographically and expressed as change in total Sharp score (TSS) and its components, the erosion score and joint space narrowing (JSN) score. Radiographs of hands/wrists and forefeet were read at baseline, 6 months, and 12 months. The results are shown in Table 3. A significant difference for change in erosion score was observed at 6 months and maintained at 12 months.

**Polyarticular-Course Juvenile Rheumatoid Arthritis (JRA)**

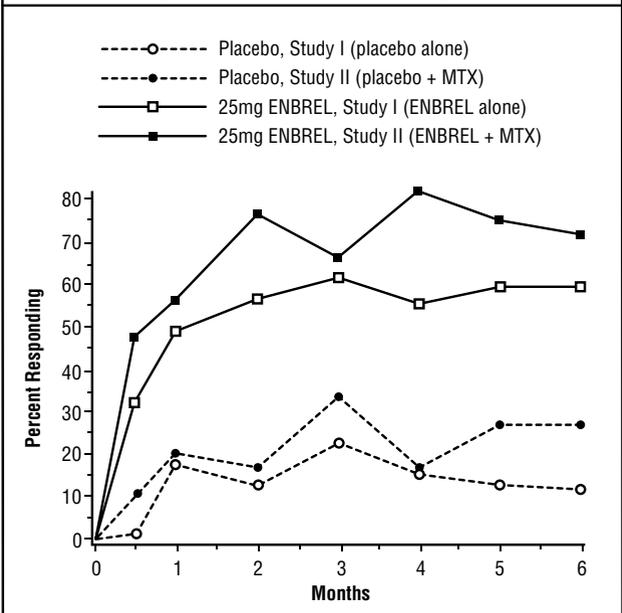
The safety and efficacy of ENBREL were assessed in a two-part study in 69 children with polyarticular-course JRA who had a variety of JRA onset types. Patients ages 4 to 17 years with moderately to severely active polyarticular-course JRA refractory to or intolerant of methotrexate were enrolled; patients remained on a stable dose of a single nonsteroidal anti-inflammatory drug and/or prednisone (≤ 0.2 mg/kg/day or 10 mg maximum). In part 1, all patients received 0.4 mg/kg (maximum 25 mg per dose) ENBREL SC twice weekly. In part 2, patients with a clinical response at day 90 were randomized to remain on ENBREL or receive placebo for four months and assessed for disease flare. Responses were measured using

**Table 1: ACR Responses in Placebo- and Active-Controlled Trials (Percent of Patients)**

Response	Placebo Controlled				Active Controlled	
	Study I		Study II		Study III	
	Placebo N = 80	ENBREL <sup>a</sup> N = 78	MTX/ Placebo N = 30	MTX/ ENBREL <sup>a</sup> N = 59	MTX N = 217	ENBREL <sup>a</sup> N = 207
<b>ACR 20</b>						
Month 3	23%	62% <sup>b</sup>	33%	66% <sup>b</sup>	56%	62%
Month 6	11%	59% <sup>b</sup>	27%	71% <sup>b</sup>	58%	65%
Month 12	NA	NA	NA	NA	65%	72%
<b>ACR 50</b>						
Month 3	8%	41% <sup>b</sup>	0%	42% <sup>b</sup>	24%	29%
Month 6	5%	40% <sup>b</sup>	3%	39% <sup>b</sup>	32%	40%
Month 12	NA	NA	NA	NA	43%	49%
<b>ACR 70</b>						
Month 3	4%	15% <sup>b</sup>	0	15% <sup>b</sup>	7%	13% <sup>c</sup>
Month 6	1%	15% <sup>b</sup>	0	15% <sup>b</sup>	14%	21% <sup>c</sup>
Month 12	NA	NA	NA	NA	22%	25%

a. 25 mg ENBREL SC twice weekly.  
 b. p < 0.01, ENBREL vs. placebo.  
 c. p < 0.05, ENBREL vs. MTX.

**Figure 1: Time Course of ACR 20 Responses**



**Table 2: Components of ACR Response in Study I**

Parameter (median)	Placebo N = 80		ENBREL <sup>a</sup> N = 78	
	Baseline	3 Months	Baseline	3 Months*
Number of tender joints <sup>b</sup>	34.0	29.5	31.2	10.0 <sup>f</sup>
Number of swollen joints <sup>c</sup>	24.0	22.0	23.5	12.6 <sup>f</sup>
Physician global assessment <sup>d</sup>	7.0	6.5	7.0	3.0 <sup>f</sup>
Patient global assessment <sup>d</sup>	7.0	7.0	7.0	3.0 <sup>f</sup>
Pain <sup>d</sup>	6.9	6.6	6.9	2.4 <sup>f</sup>
Disability index <sup>e</sup>	1.7	1.8	1.6	1.0 <sup>f</sup>
ESR (mm/hour)	31.0	32.0	28.0	15.5 <sup>f</sup>
CRP (mg/dL)	2.8	3.9	3.5	0.9 <sup>f</sup>

\* Results at 6 months showed similar improvement.

a. 25 mg ENBREL SC twice weekly.

b. Scale 0–71.

c. Scale 0–68.

d. Visual analog scale; 0 = best, 10 = worst.

e. Health Assessment Questionnaire<sup>8</sup>; 0 = best, 3 = worst; includes eight categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

f. p < 0.01, ENBREL vs. placebo, based on mean percent change from baseline.

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the JRA Definition of Improvement (DOI),<sup>10</sup> defined as  $\geq 30\%$  improvement in at least three of six and  $\geq 30\%$  worsening in no more than one of six JRA core set criteria, including active joint count, limitation of motion, physician and patient/parent global assessments, functional assessment, and ESR. Disease flare was defined as a  $\geq 30\%$  worsening in three of the six JRA core set criteria and  $\geq 30\%$  improvement in not more than one of the six JRA core set criteria and a minimum of two active joints.

In part 1 of the study, 51 of 69 (74%) patients demonstrated a clinical response and entered part 2.<sup>11</sup> In part 2, 6 of 25 (24%) patients remaining on ENBREL experienced a disease flare compared to 20 of 26 (77%)

patients receiving placebo ( $p = 0.007$ ). From the start of part 2, the median time to flare was  $\geq 116$  days for patients who received ENBREL and 28 days for patients who received placebo. Each component of the JRA core set criteria worsened in the arm that received placebo and remained stable or improved in the arm that continued on ENBREL. The data suggested the possibility of a higher flare rate among those patients with a higher baseline ESR. Of patients who demonstrated a clinical response at 90 days and entered part 2 of the study, some of the patients remaining on ENBREL continued to improve from month 3 through month 7, while those who received placebo did not improve.

The majority of JRA patients who developed a disease flare in part 2 and reintroduced ENBREL treatment up to 4 months after discontinuation re-responded to ENBREL therapy, in open-label studies. Most of the responding patients who continued ENBREL therapy without interruption have maintained responses for up to 18 months.

Studies have not been done in patients with polyarticular-course JRA to assess the effects of continued ENBREL therapy in patients who do not respond within 3 months of initiating ENBREL therapy, or to assess the combination of ENBREL with methotrexate.

### Immunogenicity

Patients were tested at multiple timepoints for antibodies to ENBREL. Antibodies to the TNF receptor portion or other protein components of the ENBREL drug product, all non-neutralizing, were detected at least once in sera of 5% of adult rheumatoid arthritis patients. No apparent correlation of antibody development to clinical response or adverse events was observed. Results from JRA patients were similar to those seen in adult RA patients treated with ENBREL. The long-term immunogenicity of ENBREL is unknown.

The data reflect the percentage of patients whose test results were considered positive for antibodies to ENBREL in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ENBREL with the incidence of antibodies to other products may be misleading.

### INDICATIONS AND USAGE

ENBREL is indicated for reducing signs and symptoms and inhibiting the progression of structural damage in patients with moderately to severely active rheumatoid arthritis. ENBREL can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone.

ENBREL is indicated for reducing signs and symptoms of moderately to severely active polyarticular-course juvenile rheumatoid arthritis in patients who have had an inadequate response to one or more DMARDs.

### CONTRAINDICATIONS

ENBREL should not be administered to patients with sepsis or with known hypersensitivity to ENBREL or any of its components.

### WARNINGS

#### INFECTIONS

**IN POST-MARKETING REPORTS, SERIOUS INFECTIONS AND SEPSIS, INCLUDING FATALITIES, HAVE BEEN REPORTED WITH THE USE OF ENBREL. MANY OF THE SERIOUS INFECTIONS HAVE OCCURRED IN PATIENTS ON CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO THEIR UNDERLYING DISEASE, COULD PREDISPOSE THEM TO INFECTIONS. RARE CASES OF TUBERCULOSIS (TB) HAVE BEEN OBSERVED IN PATIENTS TREATED WITH TNF ANTAGONISTS, INCLUDING ENBREL. PATIENTS WHO DEVELOP A NEW INFECTION WHILE UNDERGOING TREATMENT WITH ENBREL SHOULD BE MONITORED CLOSELY. ADMINISTRATION OF ENBREL SHOULD BE DISCONTINUED IF A PATIENT DEVELOPS A SERIOUS INFECTION OR SEPSIS. TREATMENT WITH ENBREL SHOULD NOT BE INITIATED IN PATIENTS WITH ACTIVE INFECTIONS INCLUDING CHRONIC OR LOCALIZED INFECTIONS. PHYSICIANS SHOULD EXERCISE CAUTION WHEN CONSIDERING THE USE OF ENBREL IN PATIENTS WITH A HISTORY OF RECURRING INFECTIONS OR WITH UNDERLYING CONDITIONS WHICH MAY PREDISPOSE PATIENTS TO INFECTIONS, SUCH AS ADVANCED OR POORLY CONTROLLED DIABETES (see PRECAUTIONS and ADVERSE REACTIONS, Infections).**

#### Neurologic Events

Treatment with ENBREL and other agents that inhibit TNF have been associated with rare cases of new onset or exacerbation of central nervous system demyelinating disorders, some presenting with mental status changes and some associated with permanent disability. Rare cases of transverse myelitis, optic neuritis, and new onset or exacerbation of seizure disorders have been observed in association with ENBREL therapy. The causal relationship to ENBREL therapy remains unclear. 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.<sup>12,13</sup> 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 treated with ENBREL. 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 to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on ENBREL. Discontinuation of ENBREL therapy should be considered in patients with confirmed significant hematologic abnormalities.

### PRECAUTIONS

#### General

Allergic reactions associated with administration of ENBREL during clinical trials have been reported in  $< 2\%$  of patients. If an anaphylactic reaction or other serious allergic reaction occurs, administration of ENBREL should be discontinued immediately and appropriate therapy initiated.

#### Information to Patients

If a patient or caregiver is to self-administer ENBREL, he/she should be instructed in injection techniques and how to measure the correct dose to help ensure the proper administration of ENBREL (see **How to Use ENBREL, Instructions for Preparing and Giving an Injection**). The first injection should be performed under the supervision of a qualified health care professional. The patient's or caregiver's

**Table 3: Mean Radiographic Change Over 6 and 12 Months in Study III**

		MTX	25 mg ENBREL	MTX-ENBREL (95% Confidence Interval*)	P-value
12 Months	Total Sharp score	1.59	1.00	0.59 (-0.12, 1.30)	0.110
	Erosion score	1.03	0.47	0.56 (0.11, 1.00)	0.002
	JSN score	0.56	0.52	0.04 (-0.39, 0.46)	0.529
6 Months	Total Sharp score	1.06	0.57	0.49 (0.06, 0.91)	0.001
	Erosion score	0.68	0.30	0.38 (0.09, 0.66)	0.001
	JSN score	0.38	0.27	0.11 (-0.14, 0.35)	0.585

\*95% confidence intervals for the differences in change scores between MTX and ENBREL

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ability to self-inject subcutaneously should be assessed. A puncture-resistant container for disposal of needles and syringes should be used. Patients and caregivers should be instructed in the technique as well as proper syringe and needle disposal, and be cautioned against reuse of these items.

## Immunosuppression

The possibility exists for anti-TNF therapies, including ENBREL, to affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 49 patients with RA treated with ENBREL, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cell populations. The impact of treatment with ENBREL on the development and course of malignancies as well as active and/or chronic infections is not fully understood (see **WARNINGS, ADVERSE REACTIONS, Infections and Malignancies**). The safety and efficacy of ENBREL in patients with immunosuppression or chronic infections have not been evaluated.

## Immunizations

No data are available on the effects of vaccination in patients receiving ENBREL. Live vaccines should not be given concurrently with ENBREL. No data are available on the secondary transmission of infection by live vaccines in patients receiving ENBREL (see **PRECAUTIONS, Immunosuppression**).

It is recommended that JRA patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating ENBREL therapy. Two JRA patients developed varicella infection and signs and symptoms of aseptic meningitis, which resolved without sequelae. Patients with a significant exposure to varicella virus should temporarily discontinue ENBREL therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

## Autoantibody Formation

Treatment with ENBREL may result in the formation of autoimmune antibodies (see **ADVERSE REACTIONS, Autoantibodies**). In post-marketing experience, rare spontaneous adverse event reports have described patients with rheumatoid factor positive RA who have developed additional autoantibodies in conjunction with rashes compatible with subacute cutaneous lupus or discoid lupus by clinical presentation and biopsy.

## Drug Interactions

Specific drug interaction studies have not been conducted with ENBREL.

## Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of ENBREL or its effect on fertility. Mutagenesis studies were conducted in vitro and in vivo, and no evidence of mutagenic activity was observed.

## Pregnancy (Category B)

Developmental toxicity studies have been performed in rats and rabbits at doses ranging from 60- to 100-fold higher than the human dose and have revealed no evidence of harm to the fetus due to ENBREL. There are, however, no studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

## Nursing Mothers

It is not known whether ENBREL is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ENBREL, a decision should be made whether to discontinue nursing or to discontinue the drug.

## Geriatric Use

A total of 197 RA patients ages 65 years or older have been studied in clinical trials. No overall differences in safety or effectiveness were observed between these patients and younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

## Pediatric Use

ENBREL is indicated for treatment of polyarticular-course juvenile rheumatoid arthritis in patients who have had an inadequate response to one or more DMARDs. For issues relevant to pediatric patients, in addition to other sections of the label, see also **WARNINGS, PRECAUTIONS, Immunizations;** and **ADVERSE REACTIONS, Adverse Reactions in Pediatric Patients**. ENBREL has not been studied in children < 4 years of age.

## ADVERSE REACTIONS

ENBREL has been studied in 1197 patients with RA, followed for up to 36 months. The proportion of patients who discontinued treatment due to adverse events was approximately 4% in both ENBREL and placebo-treated patients.

### Injection Site Reactions

In controlled trials, 37% of patients treated with ENBREL developed injection site reactions. All injection site reactions were described as mild to moderate (erythema and/or itching, pain, or swelling) and generally did not necessitate drug discontinuation. Injection site reactions generally occurred in the first month and subsequently decreased in frequency. The mean duration of injection site reactions was 3 to 5 days. Seven percent of patients experienced redness at a previous injection site when subsequent injections were given. In post-marketing experience, injection site bleeding and bruising have also been observed in conjunction with ENBREL therapy.

### Infections

In controlled trials, there were no differences in rates of infection among patients treated with ENBREL and those treated with placebo or MTX. The most common type of infection was upper respiratory infection, which occurred in 16% of placebo-treated patients and 29% of patients treated with ENBREL. When the longer observation of patients on ENBREL was accounted for, the event rate was similar in both groups.

In placebo-controlled trials in DMARD-refractory RA, no increase in the incidence of serious infections was observed (approximately 1% in both placebo and ENBREL-treated groups). The rates of infections for the ENBREL arm in Study III were similar. In all clinical trials in RA, 50 of 1197 subjects exposed to ENBREL for up to 36 months experienced serious infections, including pyelonephritis, bronchitis, septic arthritis, abdominal abscess, cellulitis, osteomyelitis, wound infection, pneumonia, foot abscess, leg ulcer, diarrhea, sinusitis, and sepsis. Serious infections, including sepsis and death, have also been reported during post-marketing use of ENBREL. Some have occurred within a few weeks after initiating treatment with ENBREL. Many of the patients had underlying conditions (e.g., diabetes, congestive heart failure, history of active or chronic infections) in addition to their rheumatoid arthritis. (See **WARNINGS**). Data from a sepsis clinical trial not specifically in patients with RA suggest that ENBREL treatment may increase mortality in patients with established sepsis.<sup>14</sup>

In post-marketing experience, infections have been observed with various pathogens including viral, bacterial, fungal, and protozoal organisms. Infections have been noted in all organ systems and have been reported in patients receiving ENBREL alone or in combination with immunosuppressive agents.

### Malignancies

Seventeen malignancies of various types were observed in 1197 RA patients treated in clinical trials with ENBREL for up to 36 months. The observed rates and incidences were similar to those expected for the population studied.

### Autoantibodies

Patients had serum samples tested for autoantibodies at multiple timepoints. In Studies I and II, the percentage of patients evaluated for antinuclear antibodies (ANA), who developed new positive ANA (titer  $\geq$  1:40) was higher in patients treated with ENBREL (11%) than in placebo-treated patients (5%). The percentage of patients who developed new positive anti-double-stranded DNA antibodies was also higher by radioimmunoassay (15% of patients treated with ENBREL compared to 4% of placebo-treated patients) and by crithidia luciliae assay (3% of patients treated with ENBREL compared to none of placebo-treated patients). The proportion of patients treated with ENBREL who developed anticardiolipin antibodies was similarly increased compared to placebo-treated patients. In Study III, no pattern of increased autoantibody

## ENBREL® (etanercept)

development was seen in ENBREL patients compared to MTX patients. No patients in placebo- and active-controlled trials developed clinical signs suggestive of a lupus-like syndrome. The impact of long-term treatment with ENBREL on the development of autoimmune diseases is unknown. In post-marketing experience, very rare spontaneous adverse event reports have described patients with rheumatoid factor positive and/or erosive RA who have developed additional autoantibodies in conjunction with rash after ENBREL therapy.

### Other Adverse Reactions

Table 4 summarizes events reported in at least 3% of all patients with higher incidence in patients treated with ENBREL compared to controls in placebo-controlled RA trials (including the combination methotrexate trial) and relevant events from Study III.

Among patients with rheumatoid arthritis treated in placebo-controlled trials, serious adverse events occurred at a frequency of 4% in 349 patients treated with ENBREL compared to 5% of 152 placebo-treated patients. In Study III, serious adverse events occurred at a frequency of 6% in 415 patients treated with ENBREL compared to 8% of 217 MTX-treated patients. Among patients with RA in placebo-controlled, active-controlled, and open-label trials of ENBREL, malignancies (see **ADVERSE REACTIONS, Malignancies**) and infections (see **ADVERSE REACTIONS, Infections**) were the most common serious adverse events observed. Other infrequent serious adverse events observed included heart failure, myocardial infarction, myocardial ischemia, cerebral ischemia, hypertension, hypotension, cholecystitis, pancreatitis, gastrointestinal hemorrhage, bursitis, depression, dyspnea, deep vein thrombosis, pulmonary embolism, membranous glomerulonephropathy, polymyositis, and thrombophlebitis.

### Adverse Reaction Information from Spontaneous Reports

Adverse events have been reported during post-approval use of ENBREL. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to ENBREL exposure.

Additional adverse events are listed by body system below:

Body as a whole:	angioedema, fatigue, fever, flu syndrome, generalized pain, weight gain
Cardiovascular:	chest pain, vasodilation (flushing)
Digestive:	altered sense of taste, anorexia, diarrhea, dry mouth, intestinal perforation
Hematologic/Lymphatic:	adenopathy, anemia, aplastic anemia, leukopenia, pancytopenia, thrombocytopenia, (see <b>WARNINGS</b> )
Musculoskeletal:	joint pain
Nervous:	paresthesias, stroke, seizures and central nervous system events suggestive of multiple sclerosis or isolated demyelinating conditions such as transverse myelitis or optic neuritis (see <b>WARNINGS</b> )
Ocular:	dry eyes, ocular inflammation
Respiratory:	dyspnea, interstitial lung disease, pulmonary disease, worsening of prior lung disorder
Skin:	cutaneous vasculitis, pruritis, subcutaneous nodules, urticaria

### Adverse Reactions in Pediatric Patients

In general, the adverse events in pediatric patients were similar in frequency and type as those seen in adult patients (see **WARNINGS** and other sections under **ADVERSE REACTIONS**). Differences from adult and other special considerations are discussed in the following paragraphs.

Severe adverse reactions reported in 69 JRA patients ages 4 to 17 years included varicella (see also **PRECAUTIONS, Immunizations**), gastroenteritis, depression/personality disorder, cutaneous ulcer, esophagitis/gastritis, group A streptococcal septic shock, type I diabetes mellitus, and soft tissue and post-operative wound infection.

Forty-three of 69 (62%) children with JRA experienced an infection while receiving ENBREL during three months of study (part 1 open-label), and the frequency and severity of infections was similar in 58 patients completing 12 months of open-label extension therapy. The types of infections reported in JRA patients were generally mild and consistent with those commonly seen in outpatient pediatric populations.

The following adverse events were reported more commonly in 69 JRA patients receiving 3 months of ENBREL compared to the 349 adult RA patients in placebo-controlled trials. These included headache (19% of patients, 1.7 events per patient year), nausea (9%, 1.0 events per patient year), abdominal pain (19%, 0.74 events per patient year), and vomiting (13%, 0.74 events per patient year).

In post-marketing experience, the following additional serious adverse events have been reported in pediatric patients: abscess with bacteremia, optic neuritis, pancytopenia, seizures, tuberculous arthritis, urinary tract infection (see **WARNINGS**), coagulopathy, cutaneous vasculitis, and transaminase elevations. The frequency of these events and their causal relationship to ENBREL therapy is unknown.

### OVERDOSAGE

The maximum tolerated dose of ENBREL has not been established in humans. Toxicology studies have been performed in monkeys at doses up to 30 times the human dose with no evidence of dose-limiting toxicities. No dose-limiting toxicities have been observed during clinical trials of ENBREL. Single IV doses up to 60 mg/m<sup>2</sup> have been administered to healthy volunteers in an endotoxemia study without evidence of dose-limiting toxicities. The highest dose level evaluated in RA patients has been a single IV loading dose of 32 mg/m<sup>2</sup> followed by SC doses of 16 mg/m<sup>2</sup> (~25 mg) administered twice weekly. In one RA trial, one patient mistakenly self-administered 62 mg ENBREL SC twice weekly for 3 weeks without experiencing adverse effects.

**Table 4: Percent of RA Patients Reporting Adverse Events in Controlled Clinical Trials\***

Event	Placebo Controlled		Active Controlled (Study III)	
	Percent of patients		Percent of patients	
	Placebo† (n = 152)	ENBREL (n = 349)	MTX (n = 217)	ENBREL (n = 415)
Injection site reaction	10	37	7	34
Infection	32	35	72	64
Non-upper respiratory infection**	32	38	60	51
Upper respiratory infection**	16	29	39	31
Headache	13	17	27	24
Nausea	10	9	29	15
Rhinitis	8	12	14	16
Dizziness	5	7	11	8
Pharyngitis	5	7	9	6
Cough	3	6	6	5
Asthenia	3	5	12	11
Abdominal pain	3	5	10	10
Rash	3	5	23	14
Peripheral edema	3	2	4	8
Respiratory disorder	1	5	NA	NA
Dyspepsia	1	4	10	11
Sinusitis	2	3	3	5
Vomiting	–	3	8	5
Mouth ulcer	1	2	14	6
Alopecia	1	1	12	6
Pneumonitis ("MTX lung")	–	–	2	0

\* Includes data from the 6-month study in which patients received concurrent MTX therapy.

† The duration of exposure for patients receiving placebo was less than the ENBREL-treated patients.

\*\* Includes data from two of the three placebo-controlled trials.

## DOSAGE AND ADMINISTRATION

The recommended dose of ENBREL for adult patients with rheumatoid arthritis is 25 mg given twice weekly as a subcutaneous injection 72–96 hours apart (see **Clinical Studies**). Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics may be continued during treatment with ENBREL. Higher doses of ENBREL have not been studied.

The recommended dose of ENBREL for pediatric patients ages 4 to 17 years with active polyarticular-course JRA is 0.4 mg/kg (up to a maximum of 25 mg per dose) given twice weekly as a subcutaneous injection 72–96 hours apart. Glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics may be continued during treatment with ENBREL. Concurrent use with methotrexate and higher doses of ENBREL have not been studied in pediatric patients.

### Preparation of ENBREL

ENBREL is intended for use under the guidance and supervision of a physician. Patients may self-inject only if their physician determines that it is appropriate and with medical follow-up, as necessary, after proper training in how to measure the correct dose and in injection technique.

**Note: The needle cover of the diluent syringe contains dry natural rubber (latex), which should not be handled by persons sensitive to this substance.**

ENBREL should be reconstituted aseptically with 1 mL of the supplied Sterile Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol) giving a solution of 1.0 mL containing 25 mg of ENBREL. During reconstitution of ENBREL, the diluent should be injected very slowly into the vial. Some foaming will occur. This is normal. To avoid excessive foaming, **do not shake or vigorously agitate**. The contents should be swirled gently during dissolution. Generally, dissolution of ENBREL takes less than 10 minutes. The reconstituted solution should be clear and colorless and used within 6 hours (see **Storage and Stability**).

Visually inspect the solution for particulate matter and discoloration prior to administration. The solution should not be used if discolored or cloudy, or if particulate matter remains. Withdraw the solution into a syringe, removing only the dose to be given from the vial. Some foam or bubbles may remain in the vial.

No other medications should be added to solutions containing ENBREL, and do not reconstitute ENBREL with other diluents. Do not filter reconstituted solution during preparation or administration.

Rotate sites for injection (thigh, abdomen, or upper arm). New injections should be given at least one inch from an old site and never into areas where the skin is tender, bruised, red, or hard. (See **How to Use ENBREL, Instructions for Preparing and Giving an Injection** instruction sheet.)

### Storage and Stability

Do not use a dose tray beyond the date stamped on the carton, dose tray label, vial label, or diluent syringe label. The dose tray containing ENBREL (sterile powder) must be refrigerated at 2–8°C (36–46°F). DO NOT FREEZE.

Administer reconstituted solutions of ENBREL as soon as possible after reconstitution. If not administered immediately after reconstitution, ENBREL may be stored in the vial at 2–8°C (36–46°F) for up to 6 hours. **ANY ENBREL NOT USED WITHIN 6 HOURS OF RECONSTITUTION SHOULD BE DISCARDED. PRODUCT STABILITY AND STERILITY CANNOT BE ASSURED.**

## HOW SUPPLIED

ENBREL is supplied in a carton containing four dose trays (NDC 58406-425-34). Each dose tray contains one 25 mg single-use vial of etanercept, one syringe (1 mL Sterile Bacteriostatic Water for Injection, USP, containing 0.9% benzyl alcohol), one plunger, and two alcohol swabs.

## Rx only

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10662-09 Issue Date 07/2001

Manufactured by:  
Immunex Corporation  
Seattle, Washington 98101  
U.S. License Number 1132  
Marketed by Immunex Corporation and  
Wyeth-Ayerst Pharmaceuticals



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5,395,760; 5,605,690; 5,945,397; Re. 36,755



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# How to Use ENBREL® (etanercept)

## INSTRUCTIONS FOR PREPARING AND GIVING AN INJECTION

## How to Use ENBREL® (etanercept)

### INSTRUCTIONS FOR PREPARING AND GIVING AN INJECTION

#### Introduction

The following instructions are for preparing and giving a dose of ENBREL. ENBREL is given as an injection under the skin. ENBREL should be used under the guidance and supervision of a doctor. Your/your child's doctor or nurse will assist you in preparing and injecting your first dose (or first few doses) of ENBREL. Do not attempt to prepare or inject ENBREL on your own until you understand how to mix and inject a dose. If you are having difficulty giving an injection, we encourage you to ask a family member or other caregiver who is able to help you with your injections to become involved with your treatment and learn how to give your injection.

**DOSING FOR PEDIATRIC PATIENTS: The appropriate dose for your child will vary depending on your child's body weight. Your child's doctor will inform you of the correct amount of drug to use.**

**SINCE THE PRODUCT WAS FIRST INTRODUCED, SERIOUS INFECTIONS, SOME INVOLVING DEATH, HAVE BEEN REPORTED IN PATIENTS USING ENBREL. MANY OF THESE INFECTIONS OCCURRED IN PATIENTS WHO WERE PRONE TO INFECTIONS, SUCH AS THOSE WITH ADVANCED OR POORLY CONTROLLED DIABETES. RARE CASES OF TUBERCULOSIS HAVE ALSO BEEN REPORTED. ENBREL SHOULD BE DISCONTINUED IN PATIENTS WITH SERIOUS INFECTIONS. DO NOT START ENBREL IF YOU HAVE AN INFECTION OF ANY TYPE OR IF YOU HAVE AN ALLERGY TO ENBREL OR ITS COMPONENTS. ENBREL SHOULD BE USED WITH CAUTION IN PATIENTS PRONE TO INFECTION. CONTACT YOUR/YOUR CHILD'S PHYSICIAN IF YOU HAVE ANY QUESTIONS ABOUT ENBREL OR INFECTIONS.**

There have been rare reports of serious nervous system disorders such as multiple sclerosis, seizures or inflammation of the nerves of the eyes. Tell your doctor if you have ever had any of these disorders or if you develop them after starting ENBREL. There have also been rare reports of serious blood disorders, some involving death. **Contact your doctor immediately if you develop symptoms such as persistent fever, bruising, bleeding, or paleness.** It is unclear if ENBREL has caused these nervous system or blood disorders. If your doctor confirms serious blood problems, you may need to stop using ENBREL.

In medical studies some people reported redness, itching, pain, swelling, bleeding and/or bruising where the injection was given (Injection Site Reactions or ISRs). If you experience any of these symptoms and they concern you, contact your/your child's doctor, nurse, or pharmacist.

The most frequent adverse events in placebo-controlled clinical trials involving 349 adults were ISR (37%), infections (35%), and headache (17%). Only the rate of ISR was higher than that of placebo. The most frequent adverse events in a methotrexate-controlled clinical trial of 415 adults with early-stage RA were infections (64%), ISR (34%), and headache (24%). Only the rate of ISR was higher than that of methotrexate. In all 1,197 RA patients studied, malignancies were rare (1%).

*NOTE: The needle cover is made from latex. If allergic to latex, talk to a doctor before using.*

ENBREL dose trays should be stored in the refrigerator at 36° to 46°F (2° to 8°C) both before and after the powder is mixed with the diluent. Solution of ENBREL (powder mixed with diluent) must be discarded if not used within 6 hours. DO NOT freeze ENBREL.

Any questions about therapy with ENBREL (for example, what to do if you miss a dose) should be directed to your/your child's doctor, nurse, or pharmacist. A toll-free information service is also available: 1-888-4ENBREL (1-888-436-2735).

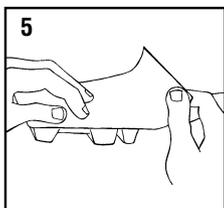
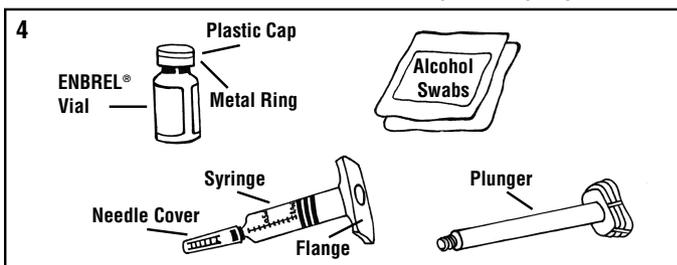
There are three methods of preparing the ENBREL dose for injection.

The first method is the *Dosing System* starter kit, which is not a part of this package, that contains tools designed to help you prepare and administer the product. Each *Dosing System* contains a "mixing station" device that helps keep the needle in line with the center of the vial stopper and guide the needle into the vial correctly. The *Dosing System* starter kit is available at no charge upon request through your/your child's doctor, or by delivery to your/your child's doctor by calling 1-888-4ENBREL. If you choose to use the "mixing station" method, follow the instructions provided in the video tape and "Step-by-Step Visual Guide" book instead of Step 3 below. The video tape and "Step-by-Step Visual Guide" book are provided with the separately available *Dosing System* starter kit.

The following instructions are for the other two methods of preparing and giving a dose of ENBREL; the free-hand method (Step 3A) or the dose preparation guide method (Step 3B). The dose preparation guide is on the underside of each dose tray provided with the product.

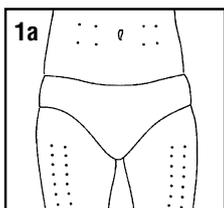
## Step 1: Setting up for an injection

1. Select a clean, well-lit, flat working surface.
2. Take the ENBREL dose tray out of the refrigerator and place it on a flat surface.
3. Wash your hands thoroughly with soap and warm water.
4. The dose tray should contain the items shown below. (If not, don't use the dose tray and consult your pharmacist.) Use only these items. The prefilled diluent syringe is specially designed for the preparation and administration of ENBREL. Do not use any other syringe.

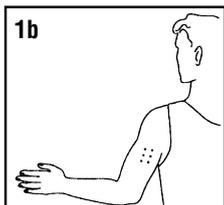


5. Peel the paper seal off the tray.
6. Inspect the expiration (Exp.) dates on both the vial label and syringe label. They should be the current month and year or later. (If not, don't use them and consult your pharmacist.)

## Step 2: Choosing and preparing an injection site



1. Choose an injection site on the thigh, stomach, or the back part of the upper arm.
2. Rotate sites with each new injection. Make sure that the new injection is given at least one inch from an old site. Do not inject into areas where the skin is tender, bruised, red, or hard. (It may be helpful to keep notes on the location of the previous injections.)



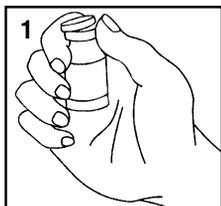
3. To prepare the area of skin where ENBREL is to be injected, wipe the injection site well with an alcohol swab, using a circular motion. **DO NOT** touch this area again before giving the injection.

### Step 3: Prepare the ENBREL dose for injection

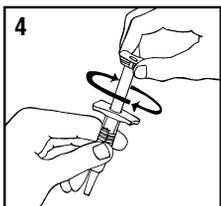
Consult your/your child's doctor about the appropriate method to use to prepare an ENBREL dose for injection. Two methods are described below.

**To use the free-hand method start with Step 3A. To use the Dose Preparation Guide method (on the underside of the dose tray) start with Step 3B.**

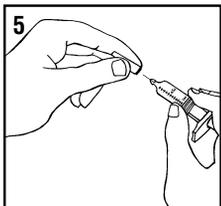
#### Step 3A: Free-hand



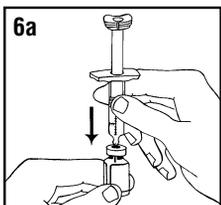
1. Remove the plastic cap from the ENBREL vial. Do not remove the gray stopper or metal ring around the top of the vial.
2. Use a new alcohol swab to clean the gray stopper on the ENBREL vial. After cleaning, place the ENBREL vial upright on a flat surface. Do not touch the stopper with your hands.
3. Slide the plunger into the syringe.



4. Turn the plunger clockwise until a slight resistance is felt. (That is, until more force is required to turn the plunger.)

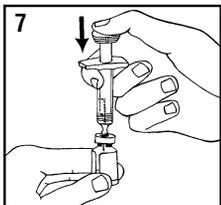
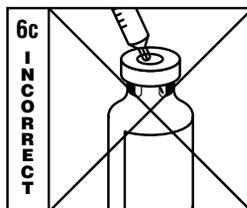
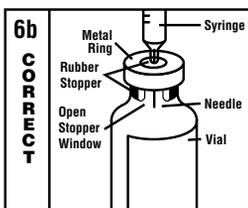


5. Pull the needle cover straight off the syringe. **DO NOT** touch the needle or allow it to touch any surface.

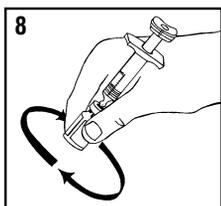


#### ADDING DILUENT

6. With the ENBREL vial upright on a flat surface, such as a table, insert the needle straight down through the center ring of the gray stopper. If the needle is correctly lined up, you should feel a slight resistance and then a "pop" as the needle goes through the center of the stopper. Look for the needle tip inside the stopper window (see Illustration 6b). If the needle is not correctly lined up with the center of the stopper, you will feel constant resistance as it goes through the stopper and no "pop." The needle may then enter at an angle and bend, break or prevent proper addition of the diluent into the vial (see illustration 6c).

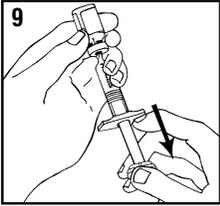


7. Push the plunger down **VERY SLOWLY** until all liquid from the syringe is in the vial. Adding the liquid too fast will cause a lot of foaming (bubbles).



8. Leave the syringe in place. Gently move or swirl the vial in circles a few times to dissolve the powder. **DO NOT SHAKE.** Wait until all the powder dissolves (usually less than 10 minutes). The solution should be clear and colorless. After the powder has completely dissolved, foam (bubbles) may still be present. This is normal. **Do not inject the solution if it contains lumps, flakes, or particles.** If all the powder in the vial is not dissolved or there are particles present, call 1-888-4ENBREL (1-888-436-2735) for assistance.

**WITHDRAWING THE ENBREL SOLUTION FROM THE VIAL**

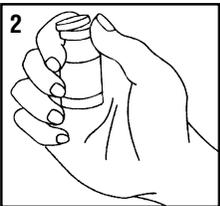


9. With the needle still in the vial, turn the vial upside down at eye level. Slowly pull the plunger back to draw the solution into the syringe. Use the “mL” markings on the side of the syringe to withdraw the appropriate dose as directed by your/your child’s doctor. For adult patients, remove the entire volume (1 mL of solution), unless otherwise directed by your doctor. For pediatric patients, remove only the portion of the 1 mL solution as directed by your child’s doctor. As the solution level drops in the vial, you may need to partially withdraw the needle to keep the tip of the needle in the solution. Some white foam may remain in the vial—this is normal.
10. With the needle still inserted in the vial, check the syringe for air bubbles. Gently tap the syringe to make any bubbles rise to the top of the syringe, near the needle. Slowly press the plunger to push the bubbles out of the syringe and into the vial. When you do this, if you accidentally push some solution back into the vial, pull slowly back on the plunger to draw the solution back into the syringe.
11. Pull the needle completely out of the vial. Again, **DO NOT** touch the needle or allow it to touch any surface.

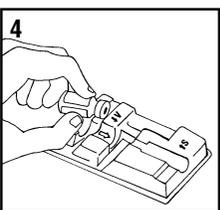
**SKIP TO STEP 4 FOR INSTRUCTIONS ON HOW TO INJECT THE ENBREL DOSE.**

**Step 3B:**  
**Dose Preparation Guide (underside of the dose tray)**

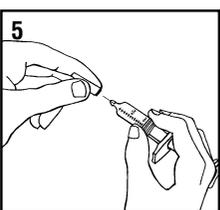
1. Remove the contents of the tray and turn the tray over. The underside of the tray is a “Dose Preparation Guide.” It is specially designed to hold the vial and syringe in place while the ENBREL solution is prepared.



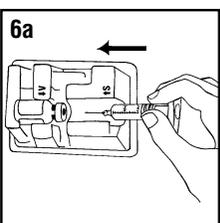
2. Remove the plastic cap from the ENBREL vial. Do not remove the gray stopper or metal ring around the top of the vial.
3. Use a new alcohol swab to clean the gray stopper on the ENBREL vial. After cleaning, do not touch the stopper with your hands.



4. Press the ENBREL vial into the space next to the ↓V mark in the Dose Preparation Guide; the gray stopper must face the center of the tray. Turn the vial so the stopper window is up and visible.

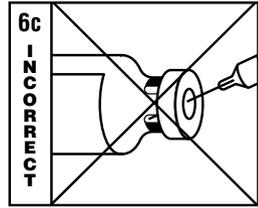
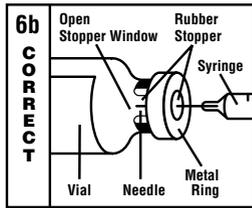


5. Pull the needle cover straight off the syringe. **DO NOT** touch the needle or allow it to touch any surface.

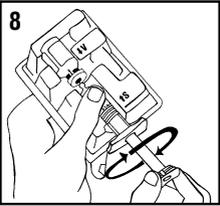


6. With the needle pointing at the gray stopper in the top of the vial, line up the “0.5 mL” mark on the syringe with the edge of the Dose Preparation Guide. Keep the syringe and needle level, so the needle does not touch the tray. Slide the syringe into the Dose Preparation Guide until the needle touches the center ring of the vial’s gray stopper. It may be necessary to rotate the vial slightly to get the needle correctly lined up with the center of the stopper. If the needle is correctly lined up, you should feel a slight resistance and then a “pop” as you push the needle through the center of the stopper. If

necessary, turn the vial again so the stopper window is up and visible. Look for the needle tip inside the stopper window (see Illustration 6b). If the needle is not correctly lined up with the center of the stopper, you will feel constant resistance as it goes through the stopper and no “pop.” The needle may then enter at an angle and bend, break or prevent proper addition of the diluent into the vial (see Illustration 6c).

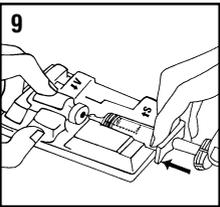


7. Slide the plunger into the syringe.
8. Turn the plunger clockwise until a slight resistance is felt. (That is, until more force is required to turn the plunger.)

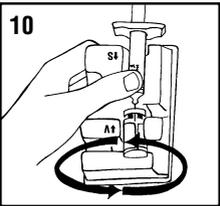


### ADDING DILUENT

9. Push the plunger down VERY SLOWLY until all the liquid from the syringe is in the vial. Adding the liquid too fast will cause a lot of foaming (bubbles).

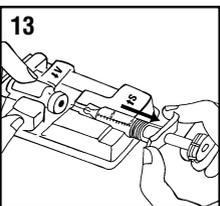
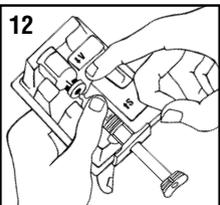
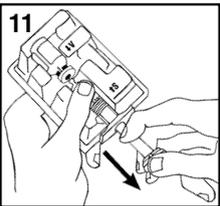


10. While holding the syringe in place, lift the Dose Preparation Guide so the vial is in an upright position. Gently move or swirl the Dose Preparation Guide in circles a few times to dissolve the powder. **DO NOT SHAKE.** Wait until all the powder dissolves (usually less than 10 minutes). The solution should be clear and colorless. After the powder has completely dissolved, foam (bubbles) may still be present. This is normal. **Do not inject the solution if it contains lumps, flakes, or particles.** If all the powder in the vial is not dissolved or there are particles present, call 1-888-4ENBREL (1-888-436-2735) for assistance.

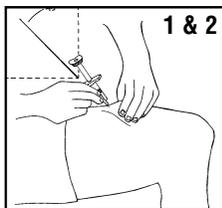


### WITHDRAWING THE ENBREL SOLUTION FROM THE VIAL

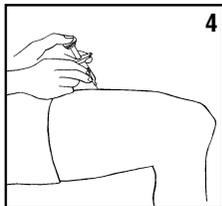
11. With the needle still in the vial, hold the Dose Preparation Guide with the vial upside down at eye level. Slowly pull the plunger back to draw the solution into the syringe. Use the “mL” markings on the side of the syringe to withdraw the appropriate dose as directed by your/your child’s doctor. For adult patients, remove the entire volume (1 mL of solution), unless otherwise directed by your doctor. For children, remove only the portion of the 1 mL solution as directed by your child’s doctor. Some white foam may remain in the vial—this is normal.
12. With the needle still inserted in the vial, check the syringe for air bubbles. Gently tap the syringe to make any bubbles rise to the top of the syringe, near the needle. Slowly press the plunger to push the bubbles out of the syringe and into the vial. When you do this, if you accidentally push some solution back into the vial, slowly pull back the plunger to draw the solution back into the syringe.
13. Slide the syringe out of the Dose Preparation Guide. Again, **DO NOT** touch the needle or allow it to touch any surface.



## Step 4: Injecting the ENBREL Solution



1. With one hand, gently pinch the cleaned area of skin and hold it firmly. With the other hand, hold the syringe at about a 45° angle to the skin.
2. With a quick, short motion, push the needle into the skin.
3. Let go of the skin with the other hand.



4. With your free hand, slowly push the plunger down to inject the drug.
5. When the syringe is empty, remove the needle from the skin, being careful to keep it at the same angle it was when it was inserted.
6. Slight bleeding may occur. If needed, press a cotton ball over the injection site for 10 seconds. Do not rub the injection site. A bandage is optional.

## Step 5: Disposing of Supplies

1. The syringe and needle should **NEVER** be reused. **NEVER** recap a needle.
2. Immediately throw away the used syringe in a puncture-resistant container. A container made specifically for disposing of used syringes and needles may be used. **DO NOT** recycle the container.
3. Keep the container out of the reach of children. When the container is about two-thirds full, dispose of it as instructed by your/your child's doctor, nurse, or pharmacist. Follow any special state or local laws regarding the proper disposal of needles and syringes.
4. ENBREL is supplied in a single-use vial that cannot be used more than once. After removing the dose needed, **any unused ENBREL should be discarded**. The ENBREL vials and used swabs should be placed in the trash, unless otherwise instructed by your/your child's doctor, nurse, or pharmacist. The dose tray and cover may be recycled.

All questions should be handled by a doctor, nurse, or pharmacist familiar with ENBREL. A toll-free information service is also available: 1-888-4ENBREL (1-888-436-2735).

Manufactured by Immunex Corporation,  
Seattle, WA 98101

Marketed by Immunex Corporation and  
Wyeth-Ayerst Pharmaceuticals



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0312-05 Issued 01/2001  
Printed in U.S.A.



This paper can be recycled

May 11, 1999

## Important Drug Warning

Dear Healthcare Professional:

This communication is to inform you of important post-marketing safety information for ENBREL<sup>®</sup> (etanercept), a new treatment for moderate to severe rheumatoid arthritis. Some of this safety information was already described in the package insert. The new information provides additional data on serious infections reported with the use of ENBREL. Over the five month period following the drug's approval in November 1998, thirty of the estimated 25,000 patients treated with ENBREL are reported to have developed serious infections including several with sepsis. Six of these patients died within two to sixteen weeks after initiation of treatment. In addition to their rheumatoid arthritis, a number of these patients had a history of chronic or recurrent infections, pre-existing infections, diabetes mellitus or other conditions that predisposed them to infections. Infections, including serious infections, are more common in the rheumatoid arthritis population than in the general public.

Based on the current information, we ask you consider the following recommendations regarding the use of ENBREL.

***Patients who develop a new infection while undergoing treatment with ENBREL should be monitored closely. Treatment with ENBREL should be discontinued in patients with serious infections, or sepsis.***

***Treatment with ENBREL should not be initiated in patients with active infections including chronic or localized infections. Physicians should exercise caution when considering the use of ENBREL in patients with a history of recurring infections or with underlying conditions, which may predispose patients to infections such as advanced or poorly controlled diabetes.***

The Warnings, Precautions, and Adverse Events sections of the labeling for ENBREL have been revised to incorporate this new information and these revised sections are included in the attached sheet.

A revised package insert is enclosed. Should you have questions regarding the use of ENBREL, please call Wyeth-Ayerst at 1-800-934-5556.

Healthcare professionals should report any serious adverse events possibly associated with the use of ENBREL to Wyeth-Ayerst at 1-800-934-5556. 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](http://www.fda.gov/medwatch), or by mail (using postage paid form) to MedWatch, IIF-2, 5600 Fishers Lane, Rockville, MD 20852-9787. Healthcare professionals and consumers should use the Form 3500 for adverse event/product problem reporting.

Sincerely,



Philip de Vane, M.D.  
Vice President, Clinical Affairs  
North American Medical Director  
Wyeth-Ayerst Laboratories



F. Ann Hayes, M.D.  
Senior Vice President  
Medical Development  
Immunex Corporation

## Revised Sections for ENBREL<sup>®</sup> (etanercept) Package Insert

### WARNINGS

**IN POST-MARKETING REPORTS, SERIOUS INFECTIONS AND SEPSIS, INCLUDING FATALITIES, HAVE BEEN REPORTED WITH THE USE OF ENBREL. MANY OF THESE SERIOUS EVENTS HAVE OCCURRED IN PATIENTS WITH UNDERLYING DISEASES THAT IN ADDITION TO THEIR RHEUMATOID ARTHRITIS COULD PREDISPOSE THEM TO INFECTIONS. PATIENTS WHO DEVELOP A NEW INFECTION WHILE UNDERGOING TREATMENT WITH ENBREL SHOULD BE MONITORED CLOSELY. ADMINISTRATION OF ENBREL SHOULD BE DISCONTINUED IF A PATIENT DEVELOPS A SERIOUS INFECTION OR SEPSIS. TREATMENT WITH ENBREL SHOULD NOT BE INITIATED IN PATIENTS WITH ACTIVE INFECTIONS INCLUDING CHRONIC OR LOCALIZED INFECTIONS. PHYSICIANS SHOULD EXERCISE CAUTION WHEN CONSIDERING THE USE OF ENBREL IN PATIENTS WITH A HISTORY OF RECURRING INFECTIONS OR WITH UNDERLYING CONDITIONS WHICH MAY PREDISPOSE PATIENTS TO INFECTIONS SUCH AS ADVANCED OR POORLY CONTROLLED DIABETES (SEE PRECAUTIONS, ADVERSE REACTIONS, Infections).**

### PRECAUTIONS

#### **Immunosuppression**

The possibility exists for anti-TNF therapies, including ENBREL, to affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 49 patients with RA treated with ENBREL, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cell populations. The impact of treatment with ENBREL on the development and course of malignancies, and active and/or chronic infections is not fully understood (see **WARNINGS, ADVERSE REACTIONS, Infections and Malignancies**). The safety and efficacy of ENBREL in patients with immunosuppression or chronic infections have not been evaluated.

## **ADVERSE REACTIONS**

### **Infections**

Upper respiratory infections (“colds”) and sinusitis were the most frequently reported infections in patients receiving ENBREL or placebo. In placebo-controlled trials, the incidence of upper respiratory tract infections was 16% in the placebo treatment group and 29% in the group treated with ENBREL; and 0.68 events per patient year in the placebo group and 0.82 events per patient year in the group treated with ENBREL when the longer observation of patients on ENBREL was accounted for.

In placebo-controlled trials evaluating ENBREL, no increase in the incidence of serious infections was observed (1.3% placebo, 0.9% ENBREL). In open-label and placebo-controlled trials, 22 serious infections were observed in a total of 745 subjects exposed to ENBREL, including: pyelonephritis, bronchitis, septic arthritis, abdominal abscess, cellulitis, osteomyelitis, wound infection, pneumonia, foot abscess, leg ulcer, diarrhea, sinusitis, and sepsis. Serious infections, including sepsis and death, have also been reported during post-marketing use of ENBREL. Some have occurred within a few weeks after initiating treatment with ENBREL. Many of the patients had underlying conditions (e.g., diabetes, congestive heart failure, history of active or chronic infections) in addition to their rheumatoid arthritis. See **WARNINGS**. Data from a sepsis clinical trial not specifically in patients with RA suggest that ENBREL treatment may increase mortality in patients with established sepsis.<sup>10</sup>



P.O. Box 8299  
Philadelphia, PA 19101-8299

**IMMUNEX®**

51 University Street  
Seattle, WA 98101-2936

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<sup>1,2</sup>. 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](http://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,



Dennis L. Parenti, M.D.  
Assistant Vice President  
Musculoskeletal, Clinical Affairs  
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. Amason 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.

**Appendix E**  
**INDIVIDUAL STUDY DESCRIPTIONS**

IMMUNEX-SPONSORED STUDIES IN NORTH AMERICA:

**Protocol 016.0018: Open-Label Extension Treatment with TNFR:Fc for Participating Patients in TNFR:Fc Clinical Trials**

This study was designed to provide all adult and pediatric arthritis patients (placebo and ENBREL treated) who have participated in clinical trials with ENBREL the opportunity to receive continued treatment. The primary objective is to evaluate the long term safety of ENBREL. This is an open label, multicenter study. Safety evaluations include: vital signs and physical exams; adverse events; serious adverse events; hematology and chemistry profiles, urinalysis; antibody formation to ENBREL; and development of autoimmune features. This study includes patients from initial licensing studies who have received ENBREL continuously for up to 5 years. ENBREL continues to be safe and effective in this population. Interim safety results from this study have been presented periodically and a manuscript describing the findings to date has recently been published (Moreland 2001). An abstract of the most recent results from this trial was also submitted for peer review and presentation at the 2001 ACR meeting (Moreland submitted).

**Protocol 016.0023: Open-Label Extension Treatment with ENBREL for Patients who participated in Immunex Clinical Trials Protocol No. 016.0012**

This study was designed to provide all RA patients (methotrexate and ENBREL treated) who have participated in the Immunex clinical trial 016.0012 (Bathon 2000) the opportunity to receive continued treatment with ENBREL. These patients received

ENBREL or methotrexate for up to 2 years. The primary objectives are to evaluate long term safety of ENBREL in patients with early stage RA and to evaluate long term radiographic progression of RA by continued monitoring of hand/wrist and foot x-ray films. Safety evaluations are as described for Protocol 016.0018.

**Protocol 016.0026: A Phase IV Registry of Etanercept in Children with Juvenile Rheumatoid Arthritis.**

This is an open-label multicenter registry for children who have a diagnosis of polyarticular course or systemic JRA. The disease onset may have been systemic, polyarticular, or pauciarticular. This study will evaluate long-term safety of ENBREL in children with polyarticular course or systemic JRA. Safety, including effects on growth and development parameters, among those who receive ENBREL will be compared to a similar cohort of patients with polyarticular course or systemic JRA who are receiving methotrexate. Four hundred patients will be enrolled on ENBREL and two hundred patients will be enrolled on methotrexate without ENBREL. Safety endpoints include

- Adverse event rates (including infection) and severity
- Growth data (height, age, weight and height velocity) will be compared between treatment cohorts and to national norms
- Occurrence of any new autoimmune disease.
- Cancer rates for each treatment cohort

**Protocol 016.0028: A Phase III Double Blind Randomized Study Comparing Etanercept (Enbrel) Combined with Methotrexate vs Methotrexate Alone in Children with Polyarticular Course Juvenile Rheumatoid Arthritis.**

This 2 part double blind, multicenter study will include 100 pediatric patients age 2 to ≤ 18 years with active polyarticular course JRA who are refractory to methotrexate.

ENBREL will be administered SC at a dose of 0.4 mg/kg (to a maximum dose of 25 mg)

twice weekly for up to 12 months. The primary safety objective is to evaluate combination therapy with ENBREL plus methotrexate vs. methotrexate alone in children with JRA.

**Protocol 016.0029: Double-blind, randomized, placebo-controlled study of ENBREL in RA patients with comorbid disorders**

Up to 70 study sites will enroll a total of 1000 patients with active RA who have comorbid diseases. The study population will be comprised of a minimum of 200 diabetics. Subjects with the other comorbidities (see below) will make up the remainder to total 1000 evaluable subjects. The primary focus will be serious infections, but all safety data will be reviewed and considered when evaluating results of this study. A Data Safety Monitoring Board (DSMB) will monitor major clinical events and safety during the course of this trial. All patients must have a documented comorbidity, including at least one of the following:

- Diabetes mellitus requiring insulin or oral hypoglycemic agents
- Chronic pulmonary disease (such as asthma or COPD)
- History of pneumonia in the last year
- Recurrent bronchitis, sinusitis, or UTI ( $\geq 2$  episodes in the previous year)

**Protocol 016.0031: A Phase 4 Study of the safety and efficacy of Etanercept in Children with Systemic Onset Juvenile Rheumatoid Arthritis**

Systemic onset juvenile rheumatoid arthritis (SOJRA) accounts for about 15% of children with JRA and is characterized by intermittent daily fevers of greater than 39.4° C with return to normal temperature between fever spikes, an evanescent rash and arthritis. This study will evaluate the safety of ENBREL in children with systemically-active SOJRA. Safety evaluations will include: medical history and review of systems, vital signs (including height and weight) and physical examinations, hematology profile, coagulating panel, chemistry profile, urinalysis, symptom/toxicity assessments, childhood behavior

checklist, autoimmune features checklist, serum for autoantibodies and anti-ENBREL antibodies.

**Protocol 016.0034: Rheumatoid Arthritis Disease Modifying Anti-Rheumatic Drug (DMARD) Intervention and Utilization Study (RADIUS 1).**

RADIUS 1 is designed to systematically collect and document use patterns, effectiveness, and safety of DMARD treatments currently used in the management of rheumatoid arthritis (RA). Five thousand patients with RA will be enrolled. It is anticipated that study data may help improve the quality of information upon which clinical decisions are based. This is a prospective, multicenter, observational study. After an initial baseline evaluation, the patient will continue to be seen at intervals deemed appropriate by his/her physician. Clinical data relevant to the routine care and management of the patient will be collected for at least 2 years.

**Protocol 016.0035: Rheumatoid Arthritis Disease Modifying Anti-Rheumatic Drug (DMARD) Intervention and Utilization Study (RADIUS 2).**

RADIUS 2 is designed to systematically collect and document prescribing patterns, effectiveness, and safety of ENBREL in the management of RA patients in clinical practice. It is anticipated that study data will provide the ability to compare the safety of Enbrel use in Radius 2 to DMARD use in RADIUS 1 and will permit further assessment of the potential confounding impact of comorbidities, concomitant medications, and disease severity in the incidence of adverse events. This is a prospective, multicenter, observational study. Five thousand patients with RA will be enrolled. Patients participating in RADIUS 1 are excluded from participation in RADIUS 2.

**Protocol 016.0620: Three month open label safety trial of ENBREL (etanercept) plus hydroxychloroquine, sulfasalazine, or injectable gold in patients with rheumatoid arthritis.**

This study will evaluate the safety of hydroxychloroquine plus ENBREL (n = 50), sulfasalazine plus ENBREL (n = 50), and gold plus ENBREL in patients with active RA (n = 20). The primary endpoint is the safety of the ENBREL combination therapy; efficacy will also be assessed.

WYETH-AYERST SPONSORED STUDIES IN EUROPE:

**Protocol 881A1-301-EU: Open-label Safety Study of Etanercept in Patients with Rheumatoid Arthritis**

This is a long-term open-label extension protocol for patients who participated in the double-blind controlled studies (881A1-100-EU & 881A1-300-EU) in Europe. A total of 549 patients have been enrolled in this multi-center study of whom 385 patients are active and have up to 3 years of exposure to ENBREL. All patients are receiving ENBREL 25 mg twice weekly. The primary objective is to evaluate the long-term safety of ENBREL. Safety evaluations include: vital signs and physical exams; adverse events; serious adverse events; hematology and chemistry profiles, urinalysis; antibody formation to ENBREL; and development of autoantibodies. ENBREL continues to be safe and effective in this population. Interim safety results from this study have been presented periodically and an abstract of the most recent results from this trial was presented at the 2001 EULAR meeting.

**DMARD Combination Studies:****Protocol 0881A1-308: A Double-Blind Study Evaluating The Efficacy and Safety of the Combination of Etanercept and Methotrexate in Comparison to Etanercept and Methotrexate Alone in Rheumatoid Arthritis.**

The objective of this study is to evaluate the therapeutic response, including radiographic changes and safety of ENBREL alone, methotrexate (MTX) alone, and the combination of ENBREL and MTX in patients with rheumatoid arthritis (RA) who have failed previous disease modifying antirheumatic drug (DMARD) therapy. Patients receive either ENBREL, 25 mg twice weekly, methotrexate, 7.5-20mg weekly or combination treatment during Period 1 which will have duration of 52 weeks. Patients will then be eligible to continue on blinded treatment in the extension phase (Period 2). The primary outcome measures are the numeric index of the ACR response area under the curve (AUC) over the first 24 weeks and the change from baseline in the total joint damage score (modified total Sharp score) over 52 weeks. Standard safety evaluations will be performed. Recruitment was completed in June 2001 for this study and 686 patients have been randomized.

**Protocol 0881A1-309: A 6-Month, Double-Blind Comparison of Etanercept, Sulphasalazine, and the Combination of Etanercept and Sulphasalazine in Patients with Active Rheumatoid Arthritis Receiving Sulphasalazine**

The objective of this study is to evaluate the therapeutic response and safety of ENBREL, sulphasalazine, and the combination of ENBREL and sulphasalazine in patients with rheumatoid arthritis (RA) who have had an inadequate response to sulphasalazine. Patients receive either ENBREL, 25 mg twice weekly, sulphasalazine, 2, 2.5 or 3 grams daily or combination treatment during Period 1 with a duration of 24 weeks. Patients will then be eligible to continue on blinded treatment in the extension phase (Period 2). The primary outcome measure is the percentage of patients achieving ACR 20% response at

week 24. Standard safety evaluations will be performed. Recruitment was completed for this study in June 2001 and 260 patients have been randomized.

**European Patient Registry:**

This study will be an extension to the already established registry in Sweden, sponsored by the Board of Health. This study currently has approximately 900 patients enrolled. This is a prospectively-designed, population-based trial where RA patients receiving ENBREL are registered and monitored continually in a structured way. The primary objective is to monitor the safety of ENBREL over a 4-year interval.