DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 103795/5125

NOV 25 2003

Immunex Corporation
Attention: Douglas Hunt
Director, Amgen Regulatory Affairs
One Amgen Center Drive
Mail Stop 24-2-C
Thousand Oaks, CA 91320-1799

Dear Mr. Hunt:

Your request to supplement your biologics license application for Etanercept to revise the Clinical Studies section of the package insert to include four-year radiographic data for rheumatoid arthritis patients has been approved.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Division of Drug Marketing, Advertising and Communication (HFD-42), Center for Drug Evaluation and Research, 5600 Fishers Lane/Room 8B45, Rockville, MD 20857. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by an FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see http://www.fda.gov/cder/biologics/default.htm. Until further notice, however, all correspondence, except as provided elsewhere in this letter, should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
Suite 200N (HFM-99)
1401 Rockville Pike
Rockville, Maryland 20852-1448

This information will be included in your biologics license application file.

Sincerely,

(b)(6)

Marc K. Walton, M.D., Ph.D.
Director
Division of Therapeutic Biological Internal Medicine Products
Office of Drug Evaluation VI
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure: package insert

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_H2 domain, the C_H3 domain and hinge region, but not the C_H1 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 (BWFI), USP (containing 0.9% benzyl alcohol). Reconstitution with the supplied BWFI yields a multiple-use, clear, and colorless solution of ENBREL® with a pH of 7.4 ± 0.3. Each 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 ankylosing spondylitis and the resulting joint pathology. Elevated levels of TNF are found in involved tissues and fluids of patients with RA, psoriatic arthritis and ankylosing spondylitis (AS).

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. 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. Etanercept

inhibits binding of both TNFα and TNFβ (lymphotoxin alpha [LTα]) to cell surface TNFRs, rendering TNF biologically inactive. Cells expressing transmembrane TNF that bind ENBREL® are not lysed in vitro in the presence or absence of complement.

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).

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 (Cmax) of 1.1 ± 0.6 mcg/mL and time to Cmax of 69 ± 34 hours was observed in these patients following a single 25 mg dose. After 6 months of twice weekly 25 mg doses in these same RA patients, the mean Cmax 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 $AUC_{0\text{-}72\ hr}$ (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.

In another study, serum concentration profiles at steady state were comparable among patients with RA treated with 50 mg ENBREL® once weekly and those treated with 25 mg ENBREL® twice weekly. The mean (± standard deviation) Cmax, Cmin, and partial AUC were 2.4 ± 1.5 mg/L, 1.2 ± 0.7 mg/L, and 297 ± 166 mg•h/L, respectively, for patients treated with 50 mg ENBREL® once weekly (N = 21); and 2.6 ± 1.2 mg/L, 1.4 ± 0.7 mg/L, and 316 ± 135 mg•h/L for patients treated with 25 mg ENBREL® twice weekly (N = 16). 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.

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. Population pharmacokinetic analyses predict that administration of 0.8 mg/kg of ENBREL® once weekly will result in Cmax 11% higher, and Cmin 20% lower at steady state as compared to administration of 0.4 mg/kg of ENBREL® twice weekly. The predicted pharmacokinetic differences between the regimens in JRA patients are of the same magnitude as the differences observed between twice weekly and weekly regimens in

adult RA patients. 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/hr, 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 in Table 1.

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/week) 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. The study was unblinded after all patients had completed at least 12 months (and a median of 17.3 months) of therapy. The majority of patients remained in the study on the treatment to which they were randomized through 2 years, after which they entered an extension study and received open-label 25 mg ENBREL®. Results from patients receiving 25 mg are presented in Table 1. 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.

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.

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

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

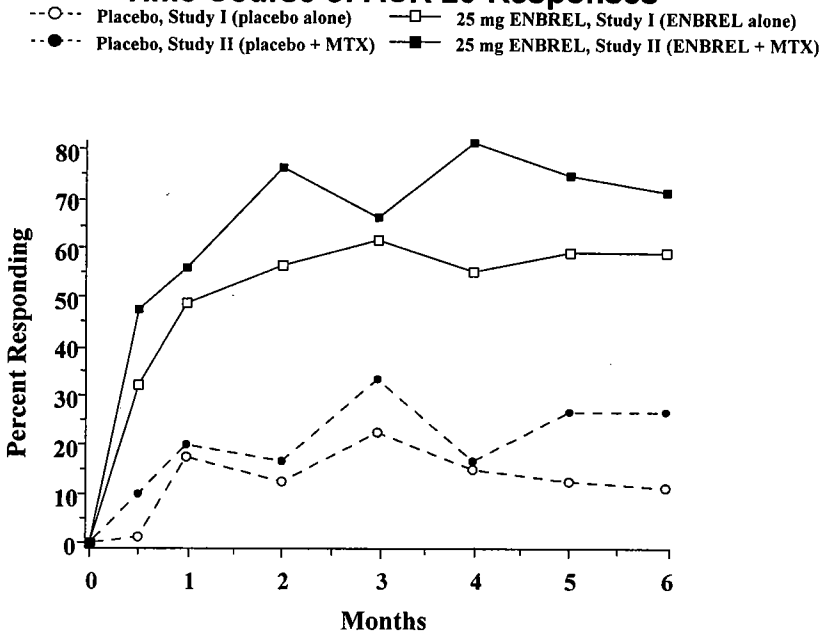
[a] 25 mg ENBREL® SC twice weekly.

[b] $p < 0.01$, ENBREL® vs. placebo.

[c] $p < 0.05$, ENBREL® vs. MTX.

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.

Figure 1:
Time Course of ACR 20 Responses



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, ACR response rates and improvement in all the individual ACR response criteria were maintained through 24 months of ENBREL® therapy. Over the 2-year study, 23% of ENBREL® patients 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. Similar results were observed for ENBREL®-treated patients in Studies II and III.

Table 2:
Components of ACR Response in Study I

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

* 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[1]; 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.

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. Some patients receiving ENBREL® for up to 3 years have been able to dose reduce and even discontinue concomitant steroids and/or methotrexate while maintaining a clinical response.

A Health Assessment Questionnaire (HAQ),[1] 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).[2] 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. Improvement in the PCS was maintained over the 24 months of ENBREL® therapy.

A 24-week study was conducted in 242 patients with active RA on background methotrexate who were randomized to receive either ENBREL® alone or the combination of ENBREL® and anakinra. The ACR_{50} response rate was 31% for patients treated with the combination of ENBREL® and anakinra and 41% for patients treated with ENBREL® alone, indicating no added clinical benefit of the combination over ENBREL® alone. Serious infections were increased with the combination compared to ENBREL® alone (see **WARNINGS**).

Physical Function Response

In Studies I, II, and III, physical function and disability were assessed using the HAQ.[1] Additionally, in Study III, patients were administered the SF-36[2] Health Survey. In Studies I and II, patients treated with 25 mg ENBREL® twice weekly showed greater improvement from baseline in the HAQ score beginning in month 1 through month 6 in comparison to placebo ($p < 0.001$) for the HAQ disability domain (where 0 = none and 3 = severe). In Study I, the mean improvement in the HAQ score from baseline to month 6 was 0.6 (from 1.6 to 1.0) for the 25 mg ENBREL® group and 0 (from 1.7 to 1.7) for the placebo group. In Study II, the mean improvement from baseline to month 6 was 0.6 (from 1.5 to 0.9) for the ENBREL®/MTX group and 0.2 (from 1.3 to 1.2) for the placebo/MTX group. In Study III, the mean improvement in the HAQ score from baseline to month 6 was 0.7 (from 1.5 to 0.7) for 25 mg ENBREL® twice weekly.

In Study III, patients treated with 25 mg ENBREL® twice weekly showed greater improvement from baseline in SF-36 physical component summary score compared to ENBREL® 10 mg twice weekly and no worsening in the SF-36 mental component summary score. In open-label ENBREL® studies, improvements in physical function and disability measures have been maintained for up to 4 years.

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 obtained at baseline, 6 months, 12 months, and 24 months and scored by readers who were unaware of treatment group. 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.

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®

Patients continued on the therapy to which they were randomized for the second year of Study III. Seventy-two percent of patients had x-rays obtained at 24 months. Compared to the patients in the MTX group, greater inhibition of progression in TSS and erosion score was seen in the 25 mg ENBREL® group, and in addition, less progression was noted in the JSN score.

In the open-label extension of Study III, 55% of the original patients treated with 25 mg ENBREL® have been evaluated radiographically at 4 years. Patients had continued inhibition of structural damage, as measured by the TSS, and 65% of them had no progression of structural damage. Patients originally treated with MTX had further reduction in radiographic progression once they began treatment with ENBREL®.

Once Weekly Dosing

The safety and efficacy of 50 mg ENBREL® (two 25 mg SC injections) administered once weekly were evaluated in a double-blind, placebo-controlled study of 420 patients with active RA. Fifty-three patients received placebo, 214 patients received 50 mg ENBREL® once weekly, and 153 patients received 25 mg ENBREL® twice weekly. The safety and efficacy profiles of the two ENBREL® treatment groups were similar.

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 the JRA Definition of Improvement (DOI),[3] defined as ≥ 30% improvement in at least three of six and ≥ 30% worsening in no

more than one of the 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 ≥ 30% worsening in three of the six JRA core set criteria and ≥ 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. 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 ≥ 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.

Psoriatic Arthritis

The safety and efficacy of ENBREL® were assessed in a randomized, double-blind, placebo-controlled study in 205 patients with psoriatic arthritis. Patients were between 18 and 70 years of age and had active psoriatic arthritis (≥ 3 swollen joints and ≥ 3 tender joints) in one or more of the following forms: (1) distal interphalangeal (DIP) involvement (N = 104); (2) polyarticular arthritis (absence of rheumatoid nodules and presence of psoriasis; N = 173); (3) arthritis mutilans (N = 3); (4) asymmetric psoriatic arthritis (N = 81); or (5) ankylosing spondylitis-like (N = 7). Patients also had plaque psoriasis with a qualifying target lesion ≥ 2 cm in diameter. Patients currently on MTX therapy (stable for ≥ 2 months) could continue at a stable dose of ≤ 25 mg/week MTX. Doses of 25 mg ENBREL® or placebo were administered SC twice a week for 6 months.

Compared to placebo, treatment with ENBREL® resulted in significant improvements in measures of disease activity (Table 4).

Table 4:

Components of Disease Activity in Psoriatic Arthritis

	Placebo N = 104		ENBREL®[a] N = 101	
Parameter (median)	Baseline	6 Months	Baseline	6 Months
Number of tender joints [b]	17.0	13.0	18.0	5.0
Number of swollen joints [c]	12.5	9.5	13.0	5.0
Physician global assessment [d]	3.0	3.0	3.0	1.0
Patient global assessment [d]	3.0	3.0	3.0	1.0
Morning stiffness (minutes)	60	60	60	15
Pain [d]	3.0	3.0	3.0	1.0
Disability index [e]	1.0	0.9	1.1	0.3
CRP (mg/dL) [f]	1.1	1.1	1.6	0.2

[a] $p < 0.001$ for all comparisons between ENBREL® and placebo at 6 months.

[b] Scale 0-78.

[c] Scale 0-76.

[d] Likert scale; 0 = best, 5 = worst.

[e] Health Assessment Questionnaire[1]; 0 = best, 3 = worst; includes eight categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

[f] Normal range: 0 - 0.79 mg/dL

Among patients with psoriatic arthritis who received ENBREL®, the clinical responses were apparent at the time of the first visit (4 weeks) and were maintained through 6 months of therapy. Responses were similar in patients who were or were not receiving concomitant methotrexate therapy at baseline. At 6 months, the ACR 20/50/70 responses were achieved by 50%, 37%, and 9%, respectively, of patients receiving ENBREL®, compared to 13%, 4%, and 1%, respectively, of patients receiving placebo. Similar responses were seen in patients with each of the subtypes of psoriatic arthritis, although few patients were enrolled with the arthritis mutilans and ankylosing spondylitis-like subtypes. The results of this study were similar to those seen in an earlier single-center, randomized, placebo-controlled study of 60 patients with psoriatic arthritis.

The skin lesions of psoriasis were also improved with ENBREL®, relative to placebo, as measured by percentages of patients achieving improvements in the Psoriasis Area and Severity Index (PASI).[4] Responses increased over time, and at 6 months, the proportions of patients achieving a 50% or 75% improvement in the PASI were 47% and 23%, respectively, in the ENBREL® group (N = 66), compared to 18% and 3%, respectively, in the placebo group (N = 62). Responses were similar in patients who were or were not receiving concomitant methotrexate therapy at baseline.

Radiographic Response

Radiographic changes were also assessed in the psoriatic arthritis study. Radiographs of hands and wrists were obtained at baseline and months 6 and 12. A modified Total Sharp Score (TSS), which included distal interphalangeal joints (i.e., not identical to the

modified TSS used for rheumatoid arthritis) was used by readers blinded to treatment group to assess the radiographs. Some radiographic features specific to psoriatic arthritis (e.g., pencil-and-cup deformity, joint space widening, gross osteolysis and ankylosis) were included in the scoring system but others (e.g., phalangeal tuft resorption, juxta-articular and shaft periostitis) were not.

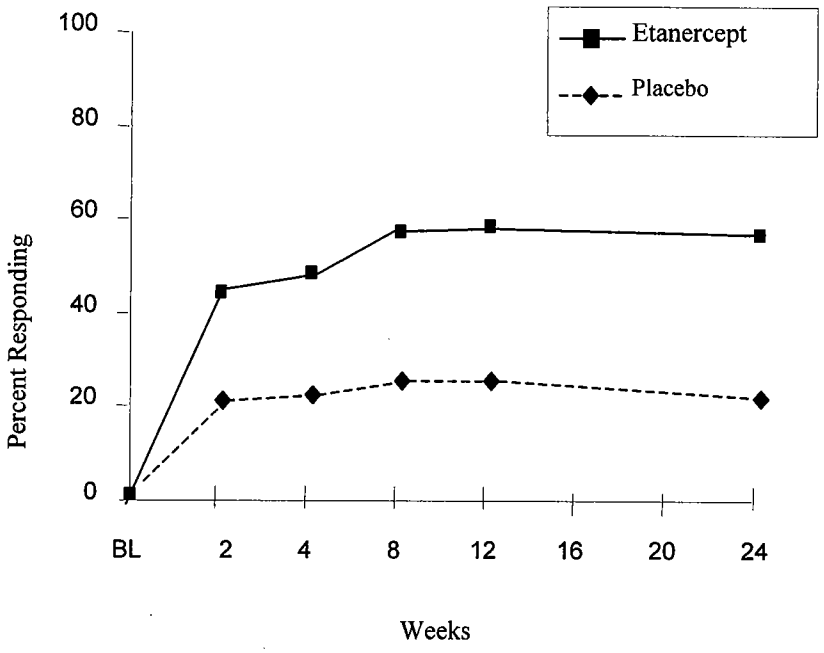
Most patients showed little or no change in the modified TSS during this 12-month study (median change of 0 in both treatment and placebo groups). However, there was a difference between groups in the distribution of scores ($p = 0.0001$, van Elteren test). More placebo-treated patients experienced larger magnitudes of radiographic worsening (increased TSS) compared to ENBREL® treatment. In an exploratory analysis, 12 of 104 placebo patients compared to 0 of 101 ENBREL®-treated patients had increases of 3 points or more in TSS.

Ankylosing Spondylitis

The safety and efficacy of ENBREL® were assessed in a randomized, double-blind, placebo-controlled study in 277 patients with active ankylosing spondylitis. Patients were between 18 and 70 years of age and had ankylosing spondylitis as defined by the modified New York Criteria for Ankylosing Spondylitis.[5] Patients were to have evidence of active disease based on values of ≥ 30 on a 0-100 unit Visual Analog Scale (VAS) for the average of morning stiffness duration and intensity, and 2 of the following 3 other parameters: a) patient global assessment, b) average of nocturnal and total back pain, and c) the average score on the Bath Ankylosing Spondylitis Functional Index (BASFI). Patients with complete ankylosis of the spine were excluded from study participation. Patients taking hydroxychloroquine, sulfasalazine, methotrexate or prednisone (≤ 10 mg/day) could continue these drugs at stable doses for the duration of the study. Doses of 25 mg ENBREL® or placebo were administered SC twice a week for 6 months.

The primary measure of efficacy was a 20% improvement in the Assessment in Ankylosing Spondylitis (ASAS) response criteria.[6] Compared to placebo, treatment with ENBREL® resulted in improvements in the ASAS and other measures of disease activity (Figure 2 and Table 5).

Figure 2: ASAS 20 Responses in Ankylosing Spondylitis



At 12 weeks, the ASAS 20/50/70 responses were achieved by 60%, 45%, and 29%, respectively, of patients receiving ENBREL®, compared to 27%, 13%, and 7%, respectively, of patients receiving placebo ($p \leq 0.0001$, ENBREL® vs. placebo). Similar responses were seen at week 24. Responses were similar between those patients receiving concomitant therapies at baseline and those who were not. The results of this study were similar to those seen in a single-center, randomized, placebo-controlled study of 40 patients and a multi-center, randomized, placebo-controlled study of 84 patients with ankylosing spondylitis.

Table 5:

Components of Ankylosing Spondylitis Disease Activity

	Placebo N = 139		ENBREL®[a] N = 138	
Mean values at time points	Baseline	6 Months	Baseline	6 Months
ASAS response criteria				
Patient global assessment [b]	63	56	63	36
Back pain [c]	62	56	60	34
BASFI [d]	56	55	52	36
Inflammation [e]	64	57	61	33
Acute phase reactants				
CRP (mg/dL) [f]	2.0	1.9	1.9	0.6
Spinal mobility (cm):				
Modified Schober's test	3.0	2.9	3.1	3.3
Chest expansion	3.2	3.0	3.3	3.9
Occiput-to-wall measurement	5.3	6.0	5.6	4.5

[a] $p < 0.0015$ for all comparisons between ENBREL® and placebo at 6 months. P-values for continuous endpoints were based on percent change from baseline.

[b] Measured on a Visual Analog Scale (VAS) scale with 0 = "none" and 100 = "severe."

[c] Average of total nocturnal and back pain scores, measured on a VAS scale with 0 = "no pain" and 100 = "most severe pain."

[d] Bath Ankylosing Spondylitis Functional Index (BASFI), average of 10 questions.

[e] Inflammation represented by the average of the last 2 questions on the 6-question Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).

[f] C-reactive protein (CRP) normal range: 0 - 1.0 mg/dL.

INDICATIONS AND USAGE

ENBREL® is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function 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.

ENBREL® is indicated for reducing signs and symptoms and inhibiting the progression of structural damage of active arthritis in patients with psoriatic 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 in patients with active ankylosing spondylitis.

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).

IN A 24-WEEK STUDY OF CONCURRENT ENBREL® AND ANAKINRA THERAPY, THE RATE OF SERIOUS INFECTIONS IN THE COMBINATION ARM (7%) WAS HIGHER THAN WITH ENBREL® ALONE (0%). THE COMBINATION OF ENBREL® AND ANAKINRA DID NOT RESULT IN HIGHER ACR RESPONSE RATES COMPARED TO ENBREL® ALONE (see CLINICAL STUDIES: Clinical Response 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. Cases of transverse myelitis, optic neuritis, multiple sclerosis, 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.[7, 8] Prescribers should exercise caution in considering the use of ENBREL® in patients with preexisting or recent-onset central nervous system demyelinating disorders (see **ADVERSE REACTIONS**).

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.

Two percent of patients treated concurrently with ENBREL® and anakinra developed neutropenia (ANC < 1 x 10^9/L). While neutropenic, one patient developed cellulitis which recovered with antibiotic therapy.

Malignancies

In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving the TNF blocker compared to control patients. During the controlled portions of ENBREL® trials, 1 lymphoma was observed among 2502 ENBREL®-treated patients versus 0 among 921 control patients (mean duration of controlled treatment approximately 6 months). In the controlled and open-label portions of clinical trials of ENBREL® in rheumatoid arthritis patients, 6 lymphomas were observed in 3389 patients over approximately 8000 patient-years of therapy. This is 2-fold higher than that expected in the general population. While patients with rheumatoid arthritis, particularly those with highly active disease, may be at a higher risk (up to several fold) for the development of lymphoma, the potential role of TNF-blocking therapy in the development of malignancies is not known (see **ADVERSE REACTIONS: Malignancies**).[11, 12]

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 for Patients

If a patient or caregiver is to administer ENBREL®, the patient or caregiver should be instructed in injection techniques and how to measure and administer the correct dose (see the ENBREL® (etanercept) "Patient Information" insert). The first injection should be performed under the supervision of a qualified health care professional. The patient's or caregiver's ability to inject subcutaneously should be assessed. Patients and caregivers should be instructed in the technique as well as proper syringe and needle disposal, and be cautioned against reuse of needles and syringes. A puncture-resistant container for disposal of needles and syringes should be used. If the product is intended for multiple use, additional syringes, needles, and alcohol swabs will be required.

Patients with Heart Failure

Two large clinical trials evaluating the use of ENBREL® in the treatment of heart failure were terminated early due to lack of efficacy. Results of one study suggested higher mortality in patients treated with ENBREL® compared to placebo. Results of the second study did not corroborate these observations. Analyses did not identify specific factors associated with increased risk of adverse outcomes in heart failure patients treated with ENBREL® (see **ADVERSE REACTIONS: Patients with Heart Failure**). There have been post-marketing reports of worsening of congestive heart failure (CHF), with and without identifiable precipitating factors, in patients taking ENBREL®. There have also been rare reports of new onset CHF, including CHF in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. Physicians should exercise caution when using ENBREL® in patients who also have heart failure, and monitor patients carefully.

Immunosuppression

Anti-TNF therapies, including ENBREL®, 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: Malignancies, ADVERSE REACTIONS: Infections,** and **Malignancies**). The safety and efficacy of ENBREL® in patients with immunosuppression or chronic infections have not been evaluated.

Immunizations

Most psoriatic arthritis patients receiving ENBREL® were able to mount effective B-cell immune responses to pneumococcal polysaccharide vaccine, but titers in aggregate were moderately lower and fewer patients had two-fold rises in titers compared to patients not receiving ENBREL®. The clinical significance of this is unknown. Patients receiving ENBREL® may receive concurrent vaccinations, except for live vaccines. 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. Patients with a significant exposure to varicella virus should temporarily discontinue ENBREL® therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

Autoimmunity

Treatment with ENBREL® may result in the formation of autoantibodies (see **ADVERSE REACTIONS: Autoantibodies**) and, rarely, in the development of a lupus-like syndrome (see **ADVERSE REACTIONS: Adverse Reaction Information from Spontaneous Reports**) which may resolve following withdrawal of ENBREL®. If a patient develops symptoms and findings suggestive of a lupus-like syndrome following treatment with ENBREL®, treatment should be discontinued and the patient should be carefully evaluated.

Drug Interactions

Specific drug interaction studies have not been conducted with ENBREL®. However, it was observed that the pharmacokinetics of ENBREL® was unaltered by concomitant methotrexate in rheumatoid arthritis patients.

In a study in which patients with active RA were treated for up to 24 weeks with concurrent ENBREL® and anakinra therapy, a 7% rate of serious infections was observed, which was higher than that observed with ENBREL® alone (0%) (see also **WARNINGS**). Two percent of patients treated concurrently with ENBREL® and anakinra developed neutropenia (ANC $< 1 \times 10^9$/L).

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 Patients with JRA.** ENBREL® has not been studied in children < 4 years of age.

ADVERSE REACTIONS

Adverse Reactions in Adult Patients with RA, Psoriatic Arthritis, or Ankylosing Spondylitis

ENBREL® has been studied in 1440 patients with RA, followed for up to 57 months, in 157 patients with psoriatic arthritis for 6 months, and in 222 patients with ankylosing spondylitis for up to 10 months. In controlled trials, the proportion of ENBREL®-treated patients who discontinued treatment due to adverse events was approximately 4% in the indications studied. The vast majority of these patients were treated with 25 mg SC twice weekly.

Injection Site Reactions

In controlled trials, approximately 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 RA, psoriatic arthritis, and ankylosing spondylitis patients treated with ENBREL® and those treated with placebo or MTX. The most common type of infection was upper respiratory infection, which occurred at a rate of approximately 20% among both ENBREL®- and placebo-treated patients.

In placebo-controlled trials in RA, psoriatic arthritis, and ankylosing spondylitis no increase in the incidence of serious infections was observed (approximately 1% in both placebo- and ENBREL®-treated groups). In all clinical trials in RA, serious infections experienced by patients have included: pyelonephritis, bronchitis, septic arthritis, abdominal abscess, cellulitis, osteomyelitis, wound infection, pneumonia, foot abscess, leg ulcer, diarrhea, sinusitis, and sepsis. The rate of serious infections has not increased in open-label extension trials and is similar to that observed in ENBREL®- and placebo-treated patients from controlled trials. 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.[9]

In patients who received both ENBREL® and anakinra for up to 24 weeks, the incidence of serious infections was 7%. The most common infections consisted of bacterial pneumonia (4 cases) and cellulitis (4 cases). One patient with pulmonary fibrosis and pneumonia died due to respiratory failure.

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

Among 3389 rheumatoid arthritis patients treated with ENBREL® in clinical trials for a mean of 28 months (approximately 8000 patient-years of therapy), 6 lymphomas were observed for a rate of 0.07 cases per 100 patient-years. This is 2-fold higher than the rate of lymphomas expected in the general population based on the Surveillance, Epidemiology, and End Results Database.[10] An increased rate of lymphoma up to several fold has been reported in the rheumatoid arthritis patient population, and may be further increased in patients with more severe disease activity[11, 12] (see **WARNINGS: Malignancies**). Fifty-five malignancies, other than lymphoma, were observed. Of these, the most common malignancies were colon, breast, lung and prostate, which were similar in type and number to what would be expected in the general population.[10] Analysis of the cancer rates at 6 month intervals suggest constant rates over three years of observation.

Immunogenicity

Patients with RA, psoriatic arthritis, or ankylosing spondylitis 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 patients with rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis. 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.

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 development was seen in ENBREL® patients compared to MTX patients.

The impact of long-term treatment with ENBREL® on the development of autoimmune diseases is unknown. Rare adverse event reports have described patients with rheumatoid factor positive and/or erosive RA who have developed additional autoantibodies in conjunction with rash and other features suggesting a lupus-like syndrome.

Other Adverse Reactions

Table 6 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. Adverse events in psoriatic arthritis and ankylosing spondylitis trials were similar to those reported in RA clinical trials.

Table 6:
Percent of RA Patients Reporting Adverse Events in Controlled Clinical Trials*

	Placebo Controlled		Active Controlled (Study III)	
	Percent of patients		Percent of patients	
Event	Placebo† (N = 152)	ENBREL® (N = 349)	MTX (N = 217)	ENBREL® (N = 415)
Injection site reaction	10	37	7	34
Infection (total)**	32	35	72	64
Non-upper respiratory infection (non-URI)**	32	38	60	51
Upper respiratory infection (URI)**	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.

** Infection (total) includes data from all three placebo-controlled trials. Non-URI and URI include data only from the two placebo-controlled trials where infections were collected separately from adverse events (placebo N = 110, ENBREL® N = 213).

In controlled trials of RA and psoriatic arthritis, rates of serious adverse events were seen at a frequency of approximately 5% among ENBREL®- and control-treated patients. Among patients with RA in placebo-controlled, active-controlled, and open-label trials of ENBREL®, malignancies (see **WARNINGS: Malignancies**, **ADVERSE REACTIONS: Malignancies**) and infections (see **ADVERSE REACTIONS: Infections**) were the most common serious adverse events observed. Other infrequent serious adverse events observed in RA, psoriatic arthritis, and ankylosing spondylitis clinical trials are listed by body system below:

Cardiovascular:	heart failure, myocardial infarction, myocardial ischemia, hypertension, hypotension, deep vein thrombosis, thrombophlebitis
Digestive:	cholecystitis, pancreatitis, gastrointestinal hemorrhage
Musculoskeletal:	bursitis, polymyositis
Nervous:	cerebral ischemia, depression, multiple sclerosis (see **WARNINGS**)
Respiratory:	dyspnea, pulmonary embolism
Urogenital:	membranous glomerulonephropathy

In a randomized controlled trial in which 51 patients with RA received ENBREL® 50 mg twice weekly and 25 patients received ENBREL® 25 mg twice weekly, the following serious adverse events were observed in the 50 mg twice weekly arm: gastrointestinal bleeding, normal pressure hydrocephalus, seizure, and stroke. No serious adverse events were observed in the 25 mg arm.

Adverse Reactions in Patients with JRA

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 adults 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 1 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. Two JRA patients developed varicella infection and signs and symptoms of aseptic meningitis which resolved without sequelae.

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 are unknown.

Patients with Heart Failure

Two randomized placebo-controlled studies have been performed in patients with CHF. In one study, patients received either ENBREL® 25 mg twice weekly, 25 mg three times weekly, or placebo. In a second study, patients received either ENBREL® 25 mg once weekly, 25 mg twice weekly, or placebo. Results of the first study suggested higher mortality in patients treated with ENBREL® at either schedule compared to placebo. Results of the second study did not corroborate these observations. Analyses did not identify specific factors associated with increased risk of adverse outcomes in heart failure patients treated with ENBREL® (see **PRECAUTIONS: Patients with Heart Failure**).

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), new-onset congestive heart failure (see **PRECAUTIONS: Patients with Heart Failure**)
Digestive:	altered sense of taste, anorexia, diarrhea, dry mouth, intestinal perforation
Hematologic/Lymphatic:	adenopathy, anemia, aplastic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia (see **WARNINGS**)
Musculoskeletal:	joint pain, lupus-like syndrome with manifestations including rash consistent with subacute or discoid lupus
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 **WARNINGS**)
Ocular:	dry eyes, ocular inflammation
Respiratory:	dyspnea, interstitial lung disease, pulmonary disease, worsening of prior lung disorder
Skin:	cutaneous vasculitis, pruritis, subcutaneous nodules, urticaria

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^2 have been administered to healthy volunteers in an endotoxemia study without evidence of dose-limiting toxicities.

DOSAGE AND ADMINISTRATION

Adult Patients

The recommended dose of ENBREL® for adult patients with rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis is 50 mg per week given as two 25 mg subcutaneous (SC) injections at separate sites. This dose should be administered as two 25 mg injections given either on the same day or 3 or 4 days apart (see **CLINICAL STUDIES**). Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics may be continued during treatment with ENBREL®. Based on a study of 50 mg ENBREL® twice weekly in patients with RA that suggested higher incidence of adverse reactions but similar ACR response rates, doses higher than 50 mg per week are not recommended (see **ADVERSE REACTIONS**).

JRA Patients

The recommended dose of ENBREL® for pediatric patients ages 4 to 17 years with active polyarticular-course JRA is 0.8 mg/kg per week (up to a maximum of 50 mg per week). The maximum dose that should be administered at a single injection site is 25 mg (1.0 mL). Therefore, for pediatric patients weighing more than 31 kg (68 pounds), the total weekly dose should be administered as two subcutaneous (SC) injections, either on the same day or 3 or 4 days apart. The dose for pediatric patients weighing 31 kg (68 pounds) or less should be administered as a single SC injection once weekly. 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 when deemed appropriate and if they receive medical follow-up, as necessary. Patients should not self-administer until they receive proper training in how to prepare and administer the correct dose.

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®.

A vial adapter is supplied for use when reconstituting the lyophilized powder. However, the vial adapter should not be used if multiple doses are going to be withdrawn from the vial. If the vial will be used for multiple doses, a 25-gauge needle should be used for reconstituting and withdrawing ENBREL®, and the supplied "Mixing Date:" sticker should be attached to the vial and the date of reconstitution entered. Reconstitution with the supplied BWFI, using a 25-gauge needle, yields a preserved, multiple-use solution that must be used within 14 days.

If using the vial adapter, twist the vial adapter onto the diluent syringe. Then, place the vial adapter over the ENBREL® vial and insert the vial adapter into the vial stopper. Push down on the plunger to inject the diluent into the ENBREL® vial. Keeping the diluent syringe in place, gently swirl the contents of the ENBREL®vial during dissolution. To avoid excessive foaming, do not shake or vigorously agitate.

If using a 25-gauge needle to reconstitute and withdraw ENBREL®, the diluent should be injected very slowly into the ENBREL® vial. It is normal for some foaming to occur. The contents should be swirled gently during dissolution. To avoid excessive foaming, do not shake or vigorously agitate.

Generally, dissolution of ENBREL® takes less than 10 minutes. 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 correct dose of reconstituted solution into the syringe. Some foam or bubbles may remain in the vial. Remove the syringe from the vial adapter or remove the 25-gauge needle from the syringe. Attach a 27-gauge needle to inject ENBREL®.

The contents of one vial of ENBREL® solution should not be mixed with, or transferred into, the contents of another vial of ENBREL®. 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.

The ENBREL® (etanercept) "Patient Information" insert contains more detailed instructions on the preparation of ENBREL®. Reconstitution with the supplied BWFI, using a 25-gauge needle, yields a preserved, multiple-use solution that must be used

within 14 days. Discard reconstituted solution after 14 days. PRODUCT STABILITY AND STERILITY CANNOT BE ASSURED AFTER 14 DAYS.

Administration of ENBREL®

Rotate sites for injection (thigh, abdomen, or upper arm). Never inject into areas where the skin is tender, bruised, red, or hard. See the ENBREL® (etanercept) "Patient Information" insert for detailed information on injection site selection and dose administration.

Storage and Stability

Do not use a dose tray beyond the expiration 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.

Reconstituted solutions of ENBREL® prepared with the supplied Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol), using a 25-gauge needle, may be stored for up to 14 days if refrigerated at 2°-8°C (36°-46°F). Discard reconstituted solution after 14 days. **PRODUCT STABILITY AND STERILITY CANNOT BE ASSURED AFTER 14 DAYS.**

HOW SUPPLIED

ENBREL® is supplied in a carton containing four dose trays (NDC 58406-425-34). Each dose tray contains one 25 mg vial of etanercept, one diluent syringe (1 mL Sterile Bacteriostatic Water for Injection, USP, containing 0.9% benzyl alcohol), one 27-gauge ½ inch needle, one vial adapter, one plunger, and two alcohol swabs. Each carton contains four "Mixing Date:" stickers.

Rx Only

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