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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_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 the resulting joint pathology.[1, 2] Elevated levels of TNF are found in the synovial fluid of RA patients and in both the synovium and psoriatic plaques of patients with psoriatic arthritis.[3, 4]

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.[5] 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.[6,7] Etanercept inhibits binding of both TNFα and TNFβ (lymphotoxin alpha [LTα]) to cell surface TNFRs, rendering TNF biologically inactive.[7] Cells expressing transmembrane TNF that bind ENBREL are not lysed in vitro in the presence or absence of complement.[7]

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).[7]

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.

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/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/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. 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. 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.[8]

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

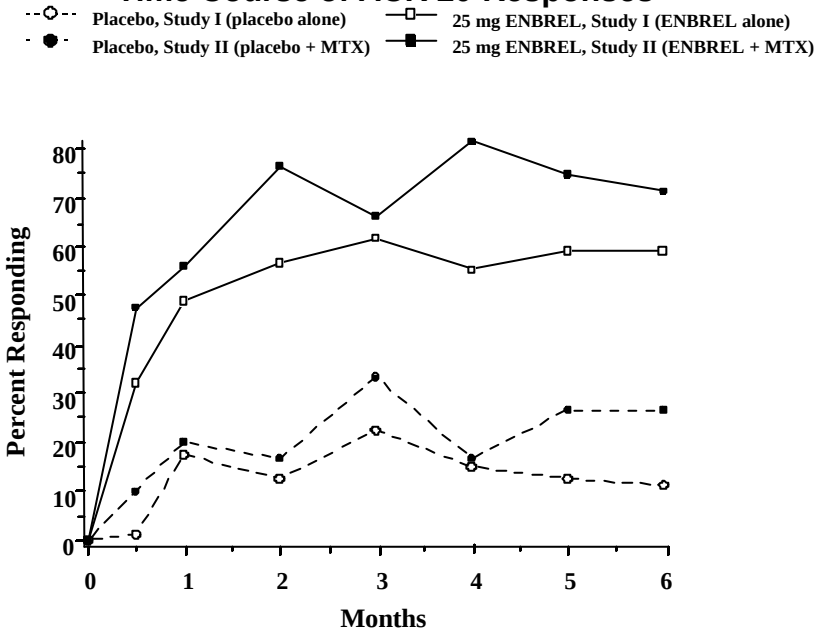
ACR Responses in Placebo- and Active-Controlled Trials

	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

	Placebo N= 80		ENBREL[a] N = 78	
Parameter (median)	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[9]; 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.

A Health Assessment Questionnaire (HAQ),[9] 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).[10] 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.

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, patients randomized to ENBREL experienced less change in TSS,

erosion score, and JSN at 24 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 the JRA Definition of Improvement (DOI),[11] 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.[12] 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 [e]	3.0	3.0	3.0	1.0
Disability index [f]	1.0	0.9	1.1	0.3
CRP (mg/dL) [g]	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. Visual analog scale; 0 = best, 10 = worst.
f. Health assessment questionnaire; 0 = best, 3 = worst; includes eight categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.
g. 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.[13]

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[14]). 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.

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.

ENBREL is indicated for reducing signs and symptoms 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.

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. 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 [15, 16]. 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.

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 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. If the product is intended for multiple-use, additional syringes, needles, and alcohol swabs will be required.

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**, **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 titres 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.

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

Adverse Reactions in Adult Patients with RA or Psoriatic Arthritis

ENBREL has been studied in approximately 1200 patients with RA, followed for up to 36 months and in 157 patients with psoriatic arthritis for 6 months. The proportion of patients who discontinued treatment due to adverse events was approximately 4% in both ENBREL and placebo-treated patients. The vast majority of these patients were treated with the recommended dose of 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 and psoriatic arthritis 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 and psoriatic arthritis, 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, 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.[17]

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.

Immunogenicity

Patients with RA or psoriatic arthritis 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 or psoriatic arthritis. 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 = 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 lucilae 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.

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 5 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 the psoriatic arthritis trial were similar to those reported in RA clinical trials.

Table 5

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 **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 and psoriatic arthritis 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 hydrocephalous, 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 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. 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.

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 **WARNINGS**)
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 **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 RA and Psoriatic Arthritis Patients

The recommended dose of ENBREL for adult patients with rheumatoid arthritis or psoriatic 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. 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 25 mg twice weekly 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 0.4 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. Reconstitution with the supplied BWFI yields a multiple-use, preservative solution that expires 14 days after reconstitution. For pediatric patients to be treated with less than a 25 mg dose, write the date in the area marked "Mixing Date:" on the supplied sticker and attach the sticker to the vial immediately after reconstitution. 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.

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.

Administration of ENBREL

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.

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 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) 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 syringe containing 1 mL Sterile Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol), one plunger, two alcohol swabs, and a dating sticker for the vial of ENBREL.

Rx only

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