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3 **ENBREL[®]**
4 **(etanercept)**

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6 For Subcutaneous Injection
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10 **DESCRIPTION**

11 ENBREL[®] (etanercept) is a dimeric fusion protein consisting of the extracellular ligand-binding
12 portion of the human 75 kilodalton (p75) tumor necrosis factor receptor (TNFR) linked to the Fc
13 portion of human IgG1. The Fc component of etanercept contains the C_H2 domain, the C_H3 domain
14 and hinge region, but not the C_H1 domain of IgG1. Etanercept is produced by recombinant DNA
15 technology in a Chinese hamster ovary (CHO) mammalian cell expression system. It consists of
16 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons.

17 ENBREL[®] is supplied in a single-use prefilled 1 mL syringe as a sterile, preservative-free solution
18 for subcutaneous injection. The solution of ENBREL[®] is clear and colorless and is formulated at
19 pH 6.3 ± 0.2. Each ENBREL[®] single-use prefilled syringe contains 0.98 mL of a 50 mg/mL
20 solution of etanercept with 10 mg/mL sucrose, 5.8 mg/mL sodium chloride, 5.3 mg/mL L-arginine
21 hydrochloride, 2.6 mg/mL sodium phosphate monobasic monohydrate and 0.9 mg/mL sodium
22 phosphate dibasic anhydrous. Administration of one 50 mg/mL prefilled syringe of ENBREL[®]
23 provides a dose equivalent to two 25 mg vials of lyophilized ENBREL[®], when vials are
24 reconstituted and administered as recommended.

25 ENBREL[®] multiple-use vial contains sterile, white, preservative-free, lyophilized powder.
26 Reconstitution with 1 mL of the supplied Sterile Bacteriostatic Water for Injection (BWFI), USP
27 (containing 0.9% benzyl alcohol) yields a multiple-use, clear, and colorless solution with a pH of
28 7.4 ± 0.3 containing 25 mg etanercept, 40 mg mannitol, 10 mg sucrose, and 1.2 mg tromethamine.

29 **CLINICAL PHARMACOLOGY**

30 **General**

31 Etanercept binds specifically to tumor necrosis factor (TNF) and blocks its interaction with cell
32 surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal
33 inflammatory and immune responses. It plays an important role in the inflammatory processes of
34 rheumatoid arthritis (RA), polyarticular-course juvenile rheumatoid arthritis (JRA), and ankylosing
35 spondylitis and the resulting joint pathology. In addition, TNF plays a role in the inflammatory
36 process of plaque psoriasis. Elevated levels of TNF are found in involved tissues and fluids of
37 patients with RA, psoriatic arthritis, ankylosing spondylitis (AS), and plaque psoriasis.

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

41 Etanercept is a dimeric soluble form of the p75 TNF receptor that can bind to two TNF molecules.
42 It inhibits the activity of TNF in vitro and has been shown to affect several animal models of
43 inflammation, including murine collagen-induced arthritis. Etanercept inhibits binding of both
44 TNF α and TNF β (lymphotoxin alpha [LT α]) to cell surface TNFRs, rendering TNF biologically
45 inactive. Cells expressing transmembrane TNF that bind ENBREL[®] are not lysed in vitro in the
46 presence or absence of complement.

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

51 **Pharmacokinetics**

52 After administration of 25 mg of ENBREL[®] by a single subcutaneous (SC) injection to 25 patients
53 with RA, a mean \pm standard deviation half-life of 102 ± 30 hours was observed with a clearance of
54 160 ± 80 mL/hr. A maximum serum concentration (C_{max}) of 1.1 ± 0.6 mcg/mL and time to C_{max}
55 of 69 ± 34 hours was observed in these patients following a single 25 mg dose. After 6 months of
56 twice weekly 25 mg doses in these same RA patients, the mean C_{max} was 2.4 ± 1.0 mcg/mL (N =
57 23). Patients exhibited a two- to seven-fold increase in peak serum concentrations and
58 approximately four-fold increase in AUC_{0-72 hr} (range 1 to 17 fold) with repeated dosing. Serum
59 concentrations in patients with RA have not been measured for periods of dosing that exceed 6
60 months. The pharmacokinetic parameters in patients with plaque psoriasis were similar to those
61 seen in patients with RA.

62 In another study, serum concentration profiles at steady state were comparable among patients with
63 RA treated with 50 mg ENBREL[®] once weekly and those treated with 25 mg ENBREL[®] twice
64 weekly. The mean (\pm standard deviation) C_{max}, C_{min}, and partial AUC were 2.4 ± 1.5 mg/L, 1.2
65 ± 0.7 mg/L, and 297 ± 166 mg•h/L, respectively, for patients treated with 50 mg ENBREL[®] once
66 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
67 with 25 mg ENBREL[®] twice weekly (N = 16).

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

71 Patients with JRA (ages 4 to 17 years) were administered 0.4 mg/kg of ENBREL[®] twice weekly for
72 up to 18 weeks. The mean serum concentration after repeated SC dosing was 2.1 mcg/mL, with a
73 range of 0.7 to 4.3 mcg/mL. Limited data suggests that the clearance of ENBREL[®] is reduced
74 slightly in children ages 4 to 8 years. Population pharmacokinetic analyses predict that
75 administration of 0.8 mg/kg of ENBREL[®] once weekly will result in C_{max} 11% higher, and C_{min}
76 20% lower at steady state as compared to administration of 0.4 mg/kg of ENBREL[®] twice weekly.
77 The predicted pharmacokinetic differences between the regimens in JRA patients are of the same

78 magnitude as the differences observed between twice weekly and weekly regimens in adult RA
79 patients. The pharmacokinetics of ENBREL[®] in children < 4 years of age have not been studied.

80 **CLINICAL STUDIES**

81 **Adult Rheumatoid Arthritis**

82 The safety and efficacy of ENBREL[®] were assessed in four randomized, double-blind, controlled
83 studies. The results of all four trials were expressed in percentage of patients with improvement in
84 RA using American College of Rheumatology (ACR) response criteria.

85 Study I evaluated 234 patients with active RA who were ≥ 18 years old, had failed therapy with at
86 least one but no more than four disease-modifying antirheumatic drugs (DMARDs; e.g.,
87 hydroxychloroquine, oral or injectable gold, methotrexate [MTX], azathioprine, D-penicillamine,
88 sulfasalazine), and had ≥ 12 tender joints, ≥ 10 swollen joints, and either ESR ≥ 28 mm/hr, CRP >
89 2.0 mg/dL, or morning stiffness for ≥ 45 minutes. Doses of 10 mg or 25 mg ENBREL[®] or placebo
90 were administered SC twice a week for 6 consecutive months. Results from patients receiving 25
91 mg are presented in Table 1.

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

97 Study III compared the efficacy of ENBREL[®] to MTX in patients with active RA. This study
98 evaluated 632 patients who were ≥ 18 years old with early (≤ 3 years disease duration) active RA;
99 had never received treatment with MTX; and had ≥ 12 tender joints, ≥ 10 swollen joints, and either
100 ESR ≥ 28 mm/hr, CRP > 2.0 mg/dL, or morning stiffness for ≥ 45 minutes. Doses of 10 mg or 25
101 mg ENBREL[®] were administered SC twice a week for 12 consecutive months. The study was
102 unblinded after all patients had completed at least 12 months (and a median of 17.3 months) of
103 therapy. The majority of patients remained in the study on the treatment to which they were
104 randomized through 2 years, after which they entered an extension study and received open-label 25
105 mg ENBREL[®]. Results from patients receiving 25 mg are presented in Table 1. MTX tablets
106 (escalated from 7.5 mg/week to a maximum of 20 mg/week over the first 8 weeks of the trial) or
107 placebo tablets were given once a week on the same day as the injection of placebo or ENBREL[®]
108 doses, respectively.

109 Study IV evaluated 682 adult patients with active RA of 6 months to 20 years duration (mean of
110 7 years) who had an inadequate response to at least one DMARD other than MTX. Forty-three
111 percent of patients had previously received MTX a mean of two years prior to the trial at a mean
112 dose of 12.9 mg. Patients were excluded from this study if MTX had been discontinued for lack of
113 efficacy or for safety considerations. The patient baseline characteristics were similar to those of
114 patients in Study I (Table 3). Patients were randomized to MTX alone (7.5 to 20 mg weekly, dose
115 escalated as described for Study III; median dose 20 mg), ENBREL[®] alone (25 mg twice weekly),
116 or the combination of ENBREL[®] and MTX initiated concurrently (at the same doses as above).
117 The study evaluated ACR response, Sharp radiographic score and safety.

118 **Clinical Response**

119 A higher percentage of patients treated with ENBREL[®] and ENBREL[®] in combination with MTX
 120 achieved ACR 20, ACR 50, and ACR 70 responses and Major Clinical Responses than in the
 121 comparison groups. The results of Studies I, II, and III are summarized in Table 1. The results of
 122 Study IV are summarized in Table 2.

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

Response	Placebo Controlled				Active Controlled	
	Study I		Study II		Study III	
	Placebo	ENBREL ^{®a}	MTX/ Placebo	MTX/ ENBREL ^{®a}	MTX	ENBREL ^{®a}
	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.

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Table 2:
Study IV Clinical Efficacy Results: Comparison of MTX vs ENBREL® vs ENBREL®
in Combination with MTX in Patients with RA
of 6 Months to 20 Years Duration
(Percent of Patients)

Endpoint	MTX (N = 228)	ENBREL® (N = 223)	ENBREL®/MTX (N = 231)
ACR N^{a, b}			
Month 12	40	47	63 ^c
ACR 20			
Month 12	59%	66%	75% ^c
ACR 50			
Month 12	36%	43%	63% ^c
ACR 70			
Month 12	17%	22%	40% ^c
Major Clinical Response^d	6%	10%	24% ^c

^a Values are medians.

^b ACR N is the percent improvement based on the same core variables used in defining ACR 20, ACR 50, and ACR 70.

^c $p < 0.05$ for comparisons of ENBREL®/MTX vs ENBREL® alone or MTX alone.

^d Major clinical response is achieving an ACR 70 response for a continuous 6-month period.

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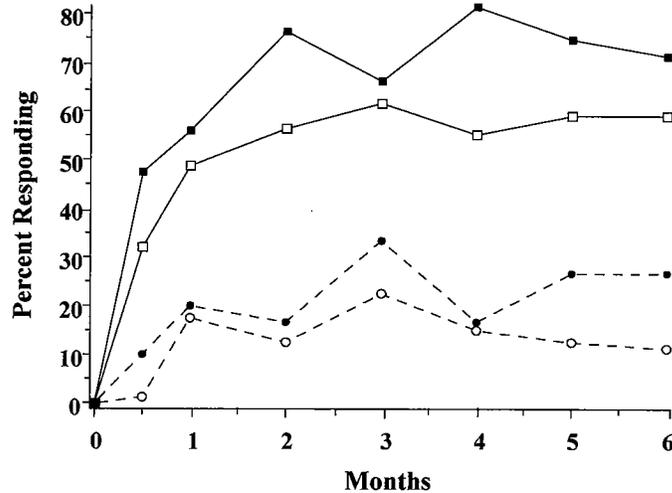
130 The time course for ACR 20 response rates for patients receiving placebo or 25 mg ENBREL® in
131 Studies I and II is summarized in Figure 1. The time course of responses to ENBREL® in Study III
132 was similar.

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

○ Placebo, Study I (placebo alone) □ 25 mg ENBREL[®], Study I (ENBREL[®] alone)
● Placebo, Study II (placebo + MTX) ■ 25 mg ENBREL[®], Study II (ENBREL[®] + MTX)



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

143 In Study III, ACR response rates and improvement in all the individual ACR response criteria were
144 maintained through 24 months of ENBREL[®] therapy. Over the 2-year study, 23% of ENBREL[®]
145 patients achieved a major clinical response, defined as maintenance of an ACR 70 response over a
146 6-month period.

147 The results of the components of the ACR response criteria for Study I are shown in Table 3.
148 Similar results were observed for ENBREL[®]-treated patients in Studies II and III.

**Table 3:
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 Questionnaire¹; 0 = best, 3 = worst; includes eight categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

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

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151 After discontinuation of ENBREL[®], symptoms of arthritis generally returned within a month.
152 Reintroduction of treatment with ENBREL[®] after discontinuations of up to 18 months resulted in
153 the same magnitudes of response as patients who received ENBREL[®] without interruption of
154 therapy based on results of open-label studies.

155 Continued durable responses were seen for over 60 months in open-label extension treatment trials
156 when patients received ENBREL[®] without interruption. A substantial number of patients who
157 initially received concomitant MTX or corticosteroids were able to reduce their doses or
158 discontinue these concomitant therapies while maintaining their clinical responses.

159 A 24-week study was conducted in 242 patients with active RA on background methotrexate who
160 were randomized to receive either ENBREL[®] alone or the combination of ENBREL[®] and anakinra.
161 The ACR50 response rate was 31% for patients treated with the combination of ENBREL[®] and
162 anakinra and 41% for patients treated with ENBREL[®] alone, indicating no added clinical benefit of
163 the combination over ENBREL[®] alone. Serious infections were increased with the combination
164 compared to ENBREL[®] alone (see **WARNINGS**).

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169 **Physical Function Response**

170 In Studies I, II, and III, physical function and disability were assessed using the Health Assessment
 171 Questionnaire (HAQ).¹ Additionally, in Study III, patients were administered the SF-36² Health
 172 Survey. In Studies I and II, patients treated with 25 mg ENBREL[®] twice weekly showed greater
 173 improvement from baseline in the HAQ score beginning in month 1 through month 6 in comparison
 174 to placebo (p < 0.001) for the HAQ disability domain (where 0 = none and 3 = severe). In Study I,
 175 the mean improvement in the HAQ score from baseline to month 6 was 0.6 (from 1.6 to 1.0) for the
 176 25 mg ENBREL[®] group and 0 (from 1.7 to 1.7) for the placebo group. In Study II, the mean
 177 improvement from baseline to month 6 was 0.6 (from 1.5 to 0.9) for the ENBREL[®]/MTX group
 178 and 0.2 (from 1.3 to 1.2) for the placebo/MTX group. In Study III, the mean improvement in the
 179 HAQ score from baseline to month 6 was 0.7 (from 1.5 to 0.7) for 25 mg ENBREL[®] twice weekly.
 180 All subdomains of the HAQ in Studies I and III were improved in patients treated with ENBREL[®].

181 In Study III, patients treated with 25 mg ENBREL[®] twice weekly showed greater improvement
 182 from baseline in SF-36 physical component summary score compared to ENBREL[®] 10 mg twice
 183 weekly and no worsening in the SF-36 mental component summary score. In open-label ENBREL[®]
 184 studies, improvements in physical function and disability measures have been maintained for up to
 185 4 years.

186 In Study IV, median HAQ scores improved from baseline levels of 1.8, 1.8, and 1.8 to 1.1, 1.0, and
 187 0.6 at 12 months in the MTX, ENBREL[®], and ENBREL[®]/MTX combination treatment groups,
 188 respectively (combination versus both MTX and ENBREL[®], p < 0.01). Twenty-nine percent of
 189 patients in the MTX alone treatment group had an improvement of HAQ of at least one unit versus
 190 40% and 51% in the ENBREL[®] alone and the ENBREL[®]/MTX combination treatment groups,
 191 respectively.

192 **Radiographic Response**

193 In Study III, structural joint damage was assessed radiographically and expressed as change in total
 194 Sharp score (TSS) and its components, the erosion score and joint space narrowing (JSN) score.
 195 Radiographs of hands/wrists and forefeet were obtained at baseline, 6 months, 12 months, and 24
 196 months and scored by readers who were unaware of treatment group. The results are shown in
 197 Table 4. A significant difference for change in erosion score was observed at 6 months and
 198 maintained at 12 months.

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Table 4:
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)	0.1
	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)	0.5
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)	0.6

* 95% confidence intervals for the differences in change scores between MTX and ENBREL[®]

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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, 48% of the original patients treated with 25 mg ENBREL[®] have been evaluated radiographically at 5 years. Patients had continued inhibition of structural damage, as measured by the TSS, and 55% 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[®].

In Study IV, less radiographic progression (TSS) was observed with ENBREL[®] in combination with MTX compared with ENBREL[®] alone or MTX alone at month 12 (Table 5). In the MTX treatment group 55% of patients experienced no radiographic progression (TSS change ≤ 0.0) at 12 months compared to 63% and 76% in the ENBREL[®] alone and the ENBREL[®]/MTX combination treatment groups, respectively.

**Table 5:
 Mean Radiographic Change in Study IV at 12 Months
 (95% Confidence Interval)**

	MTX (N = 212)*	ENBREL [®] (N = 212)*	ENBREL [®] /MTX (N = 218)*
Total Sharp Scores (TSS)	2.80 (1.08, 4.51)	0.52 ^a (-0.10, 1.15)	-0.54 ^{b,c} (-1.00, -0.07)
Erosion Score (ES)	1.68 (0.61, 2.74)	0.21 ^a (-0.20, 0.61)	-0.30 ^b (-0.65, 0.04)
Joint Space Narrowing Score (JSN)	1.12 (0.34, 1.90)	0.32 (0.00, 0.63)	-0.23 ^{b,c} (-0.45, -0.02)

* Analyzed radiographic ITT population.
^a p < 0.05 for comparison of ENBREL[®] vs MTX
^b p < 0.05 for comparison of ENBREL[®]/MTX vs MTX
^c p < 0.05 for comparison of ENBREL[®]/MTX vs ENBREL[®]

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219 **Once Weekly Dosing**

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

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

226 The safety and efficacy of ENBREL[®] were assessed in a two-part study in 69 children with
227 polyarticular-course JRA who had a variety of JRA onset types. Patients ages 4 to 17 years with
228 moderately to severely active polyarticular-course JRA refractory to or intolerant of methotrexate
229 were enrolled; patients remained on a stable dose of a single nonsteroidal anti-inflammatory drug
230 and/or prednisone (≤ 0.2 mg/kg/day or 10 mg maximum). In part 1, all patients received 0.4 mg/kg
231 (maximum 25 mg per dose) ENBREL[®] SC twice weekly. In part 2, patients with a clinical
232 response at day 90 were randomized to remain on ENBREL[®] or receive placebo for four months
233 and assessed for disease flare. Responses were measured using the JRA Definition of Improvement
234 (DOI),³ defined as $\geq 30\%$ improvement in at least three of six and $\geq 30\%$ worsening in no more
235 than one of the six JRA core set criteria, including active joint count, limitation of motion,
236 physician and patient/parent global assessments, functional assessment, and ESR. Disease flare
237 was defined as a $\geq 30\%$ worsening in three of the six JRA core set criteria and $\geq 30\%$ improvement
238 in not more than one of the six JRA core set criteria and a minimum of two active joints.

239 In part 1 of the study, 51 of 69 (74%) patients demonstrated a clinical response and entered part 2.
240 In part 2, 6 of 25 (24%) patients remaining on ENBREL[®] experienced a disease flare compared to
241 20 of 26 (77%) patients receiving placebo ($p = 0.007$). From the start of part 2, the median time to
242 flare was ≥ 116 days for patients who received ENBREL[®] and 28 days for patients who received
243 placebo. Each component of the JRA core set criteria worsened in the arm that received placebo
244 and remained stable or improved in the arm that continued on ENBREL[®]. The data suggested the
245 possibility of a higher flare rate among those patients with a higher baseline ESR. Of patients who
246 demonstrated a clinical response at 90 days and entered part 2 of the study, some of the patients
247 remaining on ENBREL[®] continued to improve from month 3 through month 7, while those who
248 received placebo did not improve.

249 The majority of JRA patients who developed a disease flare in part 2 and reintroduced ENBREL[®]
250 treatment up to 4 months after discontinuation re-responded to ENBREL[®] therapy in open-label
251 studies. Most of the responding patients who continued ENBREL[®] therapy without interruption
252 have maintained responses for up to 48 months.

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

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257 **Psoriatic Arthritis**

258 The safety and efficacy of ENBREL[®] were assessed in a randomized, double-blind,
 259 placebo-controlled study in 205 patients with psoriatic arthritis. Patients were between 18 and 70
 260 years of age and had active psoriatic arthritis (≥ 3 swollen joints and ≥ 3 tender joints) in one or
 261 more of the following forms: (1) distal interphalangeal (DIP) involvement (N = 104); (2)
 262 polyarticular arthritis (absence of rheumatoid nodules and presence of psoriasis; N = 173); (3)
 263 arthritis mutilans (N = 3); (4) asymmetric psoriatic arthritis (N = 81); or (5) ankylosing
 264 spondylitis-like (N = 7). Patients also had plaque psoriasis with a qualifying target lesion ≥ 2 cm in
 265 diameter. Patients on MTX therapy at enrollment (stable for ≥ 2 months) could continue at a stable
 266 dose of ≤ 25 mg/week MTX. Doses of 25 mg ENBREL[®] or placebo were administered SC twice a
 267 week during the initial 6-month double-blind period of the study. Patients continued to receive
 268 blinded therapy in an up to 6-month maintenance period until all patients had completed the
 269 controlled period. Following this, patients received open-label 25 mg ENBREL[®] twice a week in a
 270 12-month extension period.

271 Compared to placebo, treatment with ENBREL[®] resulted in significant improvements in measures
 272 of disease activity (Table 6).

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Table 6:
Components of Disease Activity in Psoriatic Arthritis

Parameter (median)	Placebo N = 104		ENBREL ^{®a} N = 101	
	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 Questionnaire¹; 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

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275 Among patients with psoriatic arthritis who received ENBREL[®], the clinical responses were
276 apparent at the time of the first visit (4 weeks) and were maintained through 6 months of therapy.
277 Responses were similar in patients who were or were not receiving concomitant methotrexate
278 therapy at baseline. At 6 months, the ACR 20/50/70 responses were achieved by 50%, 37%, and
279 9%, respectively, of patients receiving ENBREL[®], compared to 13%, 4%, and 1%, respectively, of
280 patients receiving placebo. Similar responses were seen in patients with each of the subtypes of
281 psoriatic arthritis, although few patients were enrolled with the arthritis mutilans and ankylosing
282 spondylitis-like subtypes. The results of this study were similar to those seen in an earlier
283 single-center, randomized, placebo-controlled study of 60 patients with psoriatic arthritis.

284 The skin lesions of psoriasis were also improved with ENBREL[®], relative to placebo, as measured
285 by percentages of patients achieving improvements in the Psoriasis Area and Severity Index
286 (PASI).⁴ Responses increased over time, and at 6 months, the proportions of patients achieving a
287 50% or 75% improvement in the PASI were 47% and 23%, respectively, in the ENBREL[®] group
288 (N = 66), compared to 18% and 3%, respectively, in the placebo group (N = 62). Responses were
289 similar in patients who were or were not receiving concomitant methotrexate therapy at baseline.

290 **Radiographic Response**

291 Radiographic changes were also assessed in the psoriatic arthritis study. Radiographs of hands and
292 wrists were obtained at baseline and months 6, 12, and 24. A modified Total Sharp Score (TSS),
293 which included distal interphalangeal joints (i.e., not identical to the modified TSS used for
294 rheumatoid arthritis) was used by readers blinded to treatment group to assess the radiographs.
295 Some radiographic features specific to psoriatic arthritis (e.g., pencil-and-cup deformity, joint space
296 widening, gross osteolysis and ankylosis) were included in the scoring system, but others (e.g.,
297 phalangeal tuft resorption, juxta-articular and shaft periostitis) were not.

298 Most patients showed little or no change in the modified TSS during this 24-month study (median
299 change of 0 in both patients who initially received ENBREL[®] or placebo). More placebo-treated
300 patients experienced larger magnitudes of radiographic worsening (increased TSS) compared to
301 ENBREL[®] treatment during the controlled period of the study. At 12 months, in an exploratory
302 analysis, 12% (12 of 104) of placebo patients compared to none of the 101 ENBREL[®]-treated
303 patients had increases of 3 points or more in TSS. Inhibition of radiographic progression was
304 maintained in patients who continued on ENBREL[®] during the second year. Of the subjects
305 patients with one-year and two-year x-rays, 3% (2 of 71) had increases of 3 points or more in TSS
306 at one and two years.

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312 **Physical Function Response**

313 In the psoriatic arthritis study, physical function and disability were assessed using the HAQ
314 Disability Index (HAQ-DI)¹ and the SF-36² Health Survey. Patients treated with 25 mg ENBREL[®]
315 twice weekly showed greater improvement from baseline in the HAQ-DI score (mean decreases of
316 54% at both months 3 and 6) in comparison to placebo (mean decreases of 6% at both months 3 and
317 6) (p <0.001). At months 3 and 6, patients treated with ENBREL[®] showed greater improvement
318 from baseline in the SF-36 physical component summary score compared to patients treated with
319 placebo, and no worsening in the SF-36 mental component summary score. Improvements in
320 physical function and disability measures were maintained for up to 2 years through the open-label
321 portion of the study.

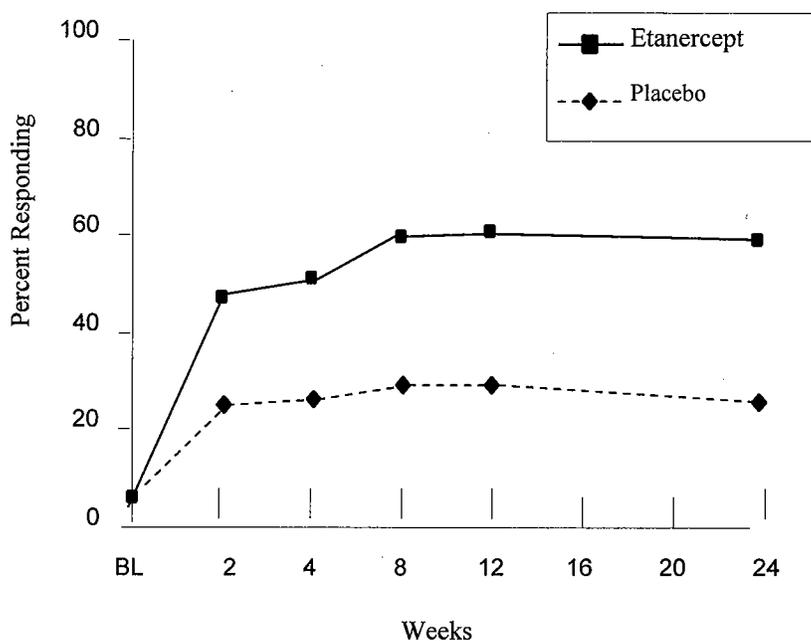
322 **Ankylosing Spondylitis**

323 The safety and efficacy of ENBREL[®] were assessed in a randomized, double-blind,
324 placebo-controlled study in 277 patients with active ankylosing spondylitis. Patients were between
325 18 and 70 years of age and had ankylosing spondylitis as defined by the modified New York
326 Criteria for Ankylosing Spondylitis.⁵ Patients were to have evidence of active disease based on
327 values of ≥ 30 on a 0-100 unit Visual Analog Scale (VAS) for the average of morning stiffness
328 duration and intensity, and 2 of the following 3 other parameters: a) patient global assessment, b)
329 average of nocturnal and total back pain, and c) the average score on the Bath Ankylosing
330 Spondylitis Functional Index (BASFI). Patients with complete ankylosis of the spine were
331 excluded from study participation. Patients taking hydroxychloroquine, sulfasalazine, methotrexate
332 or prednisone (≤ 10 mg/day) could continue these drugs at stable doses for the duration of the study.
333 Doses of 25 mg ENBREL[®] or placebo were administered SC twice a week for 6 months.

334 The primary measure of efficacy was a 20% improvement in the Assessment in Ankylosing
335 Spondylitis (ASAS) response criteria.⁶ Compared to placebo, treatment with ENBREL[®] resulted in
336 improvements in the ASAS and other measures of disease activity (Figure 2 and Table 7).

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Figure 2: ASAS 20 Responses in Ankylosing Spondylitis



360 At 12 weeks, the ASAS 20/50/70 responses were achieved by 60%, 45%, and 29%, respectively, of
361 patients receiving ENBREL[®], compared to 27%, 13%, and 7%, respectively, of patients receiving
362 placebo ($p \leq 0.0001$, ENBREL[®] vs. placebo). Similar responses were seen at week 24. Responses
363 were similar between those patients receiving concomitant therapies at baseline and those who were
364 not. The results of this study were similar to those seen in a single-center, randomized,
365 placebo-controlled study of 40 patients and a multi-center, randomized, placebo-controlled study of
366 84 patients with ankylosing spondylitis.

Table 7:
Components of Ankylosing Spondylitis Disease Activity

Mean values at time points	Placebo N = 139		ENBREL ^{®a} N = 138	
	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.

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369 **Plaque Psoriasis**

370 The safety and efficacy of ENBREL[®] were assessed in two randomized, double-blind,
371 placebo-controlled studies in adults with chronic stable plaque psoriasis involving ≥ 10% of the
372 body surface area, a minimum PASI of 10 and who had received or were candidates for systemic
373 anti-psoriatic therapy or phototherapy. Patients with guttate, erythrodermic, or pustular psoriasis
374 and patients with severe infections within 4 weeks of screening were excluded from study. No
375 concomitant major anti-psoriatic therapies were allowed during the study.

376 Study I evaluated 672 patients who received placebo or ENBREL[®] SC at doses of 25 mg once a
377 week, 25 mg twice a week or 50 mg twice a week for 3 months. After 3 months, patients continued
378 on blinded treatments for an additional 3 months during which time, patients originally randomized
379 to placebo began treatment with blinded ENBREL[®] at 25 mg twice weekly (designated as
380 placebo/ENBREL[®] in Table 8); patients originally randomized to ENBREL[®] continued on the
381 originally randomized dose (designated as ENBREL[®]/ENBREL[®] groups in Table 8).

382 Study II evaluated 611 patients who received placebo or ENBREL[®] SC at doses of 25 mg or 50 mg
383 twice a week for 3 months. After 3 months of randomized blinded treatment, patients in all three
384 arms began receiving open-label ENBREL[®] at 25 mg twice weekly for 9 additional months.

385 Response to treatment in both studies was assessed after 3 months of therapy and was defined as the
386 proportion of patients who achieved a reduction in score of at least 75% from baseline by the Psoriasis
387 Area and Severity Index (PASI). The PASI is a composite score that takes into consideration both the
388 fraction of body surface area affected and the nature and severity of psoriatic changes within the
389 affected regions (induration, erythema, and scaling).

390 Other evaluated outcomes included the proportion of patients who achieved a score of “clear” or
391 “minimal” by the Static Physician Global Assessment (sPGA) and the proportion of patients with a
392 reduction of PASI of at least 50% from baseline. The sPGA is a 6 category scale ranging from “5 =
393 severe” to “0 = none” indicating the physician’s overall assessment of the psoriasis severity focusing
394 on induration, erythema, and scaling. Treatment success of “clear” or “minimal” consisted of none or
395 minimal elevation in plaque, up to faint red coloration in erythema, and none or minimal fine scale
396 over < 5% of the plaque.

397 Patients in all treatment groups and in both studies had a median baseline PASI score ranging from
398 15 to 17; and the percentage of patients with baseline sPGA classifications ranged from 54% to
399 66% for moderate, 17% to 26% for marked, and 1% to 5% for severe. Across all treatment groups,
400 the percentage of patients who previously received systemic therapy for psoriasis ranged from 61%
401 to 65% in Study I, and 71% to 75% in Study II; and those who previously received phototherapy
402 ranged from 44% to 50% in Study I, and 72% to 73% in Study II.

403 More patients randomized to ENBREL[®] than placebo achieved at least a 75% reduction from
404 baseline PASI score (PASI 75) with a dose response relationship across doses of 25 mg once a
405 week, 25 mg twice a week and 50 mg twice a week (Tables 8 and 9). The individual components
406 of the PASI (induration, erythema, and scaling) contributed comparably to the overall treatment-
407 associated improvement in PASI.

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Table 8: Study I Outcomes at 3 and 6 Months

	Placebo/ENBREL [®] 25 mg BIW (N = 168)	ENBREL [®] /ENBREL [®]		
		25 mg QW (N = 169)	25 mg BIW (N = 167)	50 mg BIW (N = 168)
3 Months				
PASI 75 n (%)	6 (4%)	23 (14%) ^a	53 (32%) ^b	79 (47%) ^b
Difference (95% CI)		10% (4, 16)	28% (21, 36)	43% (35, 52)
sPGA, “clear” or “minimal” n (%)	8 (5%)	36 (21%) ^b	53 (32%) ^b	79 (47%) ^b
Difference (95% CI)		17% (10, 24)	27% (19, 35)	42% (34, 50)
PASI 50 n (%)	24 (14%)	62 (37%) ^b	90 (54%) ^b	119 (71%) ^b
Difference (95% CI)		22% (13, 31)	40% (30, 49)	57% (48, 65)
6 Months				
PASI 75 n (%)	55 (33%)	36 (21%)	68 (41%)	90 (54%)

^a p = 0.001 compared with placebo^b p < 0.0001 compared with placebo

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Table 9: Study II Outcomes at 3 Months

	Placebo (N = 204)	ENBREL [®]	
		25 mg BIW (N = 204)	50 mg BIW (N = 203)
PASI 75 n (%)	6 (3%)	66 (32%) ^a	94 (46%) ^a
Difference (95% CI)		29% (23, 36)	43% (36, 51)
sPGA “clear” or “minimal” n (%)	7 (3%)	75 (37%) ^a	109 (54%) ^a
Difference (95% CI)		34% (26, 41)	50 (43, 58)
PASI 50 n (%)	18 (9%)	124 (61%) ^a	147 (72%) ^a
Difference (95% CI)		52% (44, 60)	64% (56, 71)

^a p < 0.0001 compared with placebo

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415 Among PASI 75 achievers in both studies, the median time to PASI 50 and PASI 75 was
 416 approximately 1 and approximately 2 months, respectively, after the start of therapy with either 25
 417 or 50 mg twice a week.

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419 In Study I patients who achieved PASI 75 at month 6 were entered into a study drug withdrawal and
420 retreatment period. Following withdrawal of study drug, these patients had a median duration of
421 PASI 75 of between 1 and 2 months.

422 In Study I, in patients who were PASI 75 responders at 3 months, retreatment with open-label
423 ENBREL[®] after discontinuation of up to 5 months resulted in a similar proportion of responders as
424 was seen during the initial double-blind portion of the study.

425 In Study II, most patients initially randomized to 50 mg twice a week continued in the study after
426 month 3 and had their ENBREL[®] dose decreased to 25 mg twice a week. Of the 91 patients who
427 were PASI 75 responders at month 3, 70 (77%) maintained their PASI 75 response at month 6.

428 Efficacy and safety of ENBREL[®] treatment beyond 12 months has not been adequately evaluated in
429 patients with psoriasis.

430 **INDICATIONS AND USAGE**

431 ENBREL[®] is indicated for reducing signs and symptoms, inducing major clinical response,
432 inhibiting the progression of structural damage, and improving physical function in patients with
433 moderately to severely active rheumatoid arthritis. ENBREL[®] can be initiated in combination with
434 methotrexate (MTX) or used alone.

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

438 ENBREL[®] is indicated for reducing signs and symptoms, inhibiting the progression of structural
439 damage of active arthritis, and improving physical function in patients with psoriatic arthritis.
440 ENBREL[®] can be used in combination with methotrexate in patients who do not respond
441 adequately to methotrexate alone.

442 ENBREL[®] is indicated for reducing signs and symptoms in patients with active ankylosing
443 spondylitis.

444 ENBREL[®] is indicated for the treatment of adult patients (18 years or older) with chronic moderate
445 to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

446 **CONTRAINDICATIONS**

447 ENBREL[®] should not be administered to patients with sepsis or with known hypersensitivity to
448 ENBREL[®] or any of its components.

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453 **WARNINGS**

454 **INFECTIONS**

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

472 **IN A 24-WEEK STUDY OF CONCURRENT ENBREL® AND ANAKINRA THERAPY,**
473 **THE RATE OF SERIOUS INFECTIONS IN THE COMBINATION ARM (7%) WAS**
474 **HIGHER THAN WITH ENBREL® ALONE (0%). THE COMBINATION OF ENBREL®**
475 **AND ANAKINRA DID NOT RESULT IN HIGHER ACR RESPONSE RATES**
476 **COMPARED TO ENBREL® ALONE (see CLINICAL STUDIES: Clinical Response and**
477 **ADVERSE REACTIONS: Infections). CONCURRENT THERAPY WITH ENBREL® AND**
478 **ANAKINRA IS NOT RECOMMENDED.**

479 **Neurologic Events**

480 Treatment with ENBREL® and other agents that inhibit TNF have been associated with rare cases
481 of new onset or exacerbation of central nervous system demyelinating disorders, some presenting
482 with mental status changes and some associated with permanent disability. Cases of transverse
483 myelitis, optic neuritis, multiple sclerosis, and new onset or exacerbation of seizure disorders have
484 been observed in association with ENBREL® therapy. The causal relationship to ENBREL®
485 therapy remains unclear. While no clinical trials have been performed evaluating ENBREL®
486 therapy in patients with multiple sclerosis, other TNF antagonists administered to patients with
487 multiple sclerosis have been associated with increases in disease activity.^{7,8} Prescribers should
488 exercise caution in considering the use of ENBREL® in patients with preexisting or recent-onset
489 central nervous system demyelinating disorders (see **ADVERSE REACTIONS**).

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492 Hematologic Events

493 Rare reports of pancytopenia including aplastic anemia, some with a fatal outcome, have been
494 reported in patients treated with ENBREL[®]. The causal relationship to ENBREL[®] therapy remains
495 unclear. Although no high risk group has been identified, caution should be exercised in patients
496 being treated with ENBREL[®] who have a previous history of significant hematologic abnormalities.
497 All patients should be advised to seek immediate medical attention if they develop signs and
498 symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding,
499 pallor) while on ENBREL[®]. Discontinuation of ENBREL[®] therapy should be considered in
500 patients with confirmed significant hematologic abnormalities.

501 Two percent of patients treated concurrently with ENBREL[®] and anakinra developed neutropenia
502 (ANC < 1 x 10⁹/L). While neutropenic, one patient developed cellulitis which recovered with
503 antibiotic therapy.

504 Malignancies

505 In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma
506 have been observed among patients receiving the TNF blocker compared to control patients.
507 During the controlled portions of ENBREL[®] trials, 3 lymphomas were observed among 4509
508 ENBREL[®]-treated patients versus 0 among 2040 control patients (duration of controlled treatment
509 ranged from 3 to 24 months). In the controlled and open-label portions of clinical trials of
510 ENBREL[®], 9 lymphomas were observed in 5723 patients over approximately 11201 patient-years
511 of therapy. This is 3-fold higher than that expected in the general population. While patients with
512 rheumatoid arthritis or psoriasis, particularly those with highly active disease, may be at a higher
513 risk (up to several fold) for the development of lymphoma, the potential role of TNF-blocking
514 therapy in the development of malignancies is not known (see **ADVERSE REACTIONS:**
515 **Malignancies**).^{11, 12}

516 PRECAUTIONS

517 General

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

521 Caution: The needle cover of the prefilled syringe contains natural rubber (latex) which may cause
522 allergic reactions in individuals sensitive to this substance.

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527 **Information for Patients**

528 ENBREL[®] is provided as a single-use prefilled syringe or multiple-use vial. The needle cover on
529 the single-use prefilled syringe contains dry natural rubber (latex), which should not be handled by
530 persons sensitive to this substance. If a patient or caregiver is to administer ENBREL[®], the patient
531 or caregiver should be instructed in injection techniques and how to measure and administer the
532 correct dose (see the ENBREL[®] (etanercept) “Patient Information” insert). The first injection
533 should be performed under the supervision of a qualified health care professional. The patient’s or
534 caregiver’s ability to inject subcutaneously should be assessed. Patients and caregivers should be
535 instructed in the technique as well as proper syringe and needle disposal, and be cautioned against
536 reuse of needles and syringes. A puncture-resistant container for disposal of needles and syringes
537 should be used. If the product is intended for multiple use, additional syringes, needles, and alcohol
538 swabs will be required.

539 **Patients with Heart Failure**

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

551 **Immunosuppression**

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

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565 **Immunizations**

566 Most psoriatic arthritis patients receiving ENBREL[®] were able to mount effective B-cell immune
567 responses to pneumococcal polysaccharide vaccine, but titers in aggregate were moderately lower
568 and fewer patients had two-fold rises in titers compared to patients not receiving ENBREL[®]. The
569 clinical significance of this is unknown. Patients receiving ENBREL[®] may receive concurrent
570 vaccinations, except for live vaccines. No data are available on the secondary transmission of
571 infection by live vaccines in patients receiving ENBREL[®] (see **PRECAUTIONS:**
572 **Immunosuppression**).

573 It is recommended that JRA patients, if possible, be brought up to date with all immunizations in
574 agreement with current immunization guidelines prior to initiating ENBREL[®] therapy. Patients
575 with a significant exposure to varicella virus should temporarily discontinue ENBREL[®] therapy and
576 be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

577 **Autoimmunity**

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

584 **Drug Interactions**

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

588 In a study in which patients with active RA were treated for up to 24 weeks with concurrent
589 ENBREL[®] and anakinra therapy, a 7% rate of serious infections was observed, which was higher
590 than that observed with ENBREL[®] alone (0%) (see also **WARNINGS**). Two percent of patients
591 treated concurrently with ENBREL[®] and anakinra developed neutropenia (ANC < 1 x 10⁹/L).

592 **Carcinogenesis, Mutagenesis, and Impairment of Fertility**

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

596 **Pregnancy (Category B)**

597 Developmental toxicity studies have been performed in rats and rabbits at doses ranging from 60- to
598 100-fold higher than the human dose and have revealed no evidence of harm to the fetus due to
599 ENBREL[®]. There are, however, no studies in pregnant women. Because animal reproduction
600 studies are not always predictive of human response, this drug should be used during pregnancy
601 only if clearly needed.

602 **Nursing Mothers**

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

607 **Geriatric Use**

608 A total of 480 RA patients and 89 plaque psoriasis patients ages 65 years or older have been studied
609 in clinical trials. No overall differences in safety or effectiveness were observed between these
610 patients and younger patients. Because there is a higher incidence of infections in the elderly
611 population in general, caution should be used in treating the elderly.

612 **Pediatric Use**

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

618 The safety and efficacy of ENBREL[®] in pediatric patients with plaque psoriasis have not been
619 studied.

620 **ADVERSE REACTIONS**

621 **Adverse Reactions in Adult Patients with RA, Psoriatic Arthritis, Ankylosing**
622 **Spondylitis, or Plaque Psoriasis**

623 ENBREL[®] has been studied in 1442 patients with RA, followed for up to 80 months, in 169
624 patients with psoriatic arthritis for up to 24 months, in 222 patients with ankylosing spondylitis for
625 up to 10 months, and 1261 patients with plaque psoriasis for up to 15 months. In controlled trials,
626 the proportion of ENBREL[®]-treated patients who discontinued treatment due to adverse events was
627 approximately 4% in the indications studied. The vast majority of these patients were treated with
628 25 mg SC twice weekly. In plaque psoriasis studies, ENBREL[®] doses studied were 25 mg SC once
629 a week, 25 mg SC twice a week, and 50 mg SC twice a week.

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636 **Injection Site Reactions**

637 In controlled trials in rheumatologic indications, approximately 37% of patients treated with
638 ENBREL[®] developed injection site reactions. In controlled trials in patients with plaque psoriasis,
639 14% of patients treated with ENBREL[®] developed injection site reactions during the first 3 months
640 of treatment. All injection site reactions were described as mild to moderate (erythema and/or
641 itching, pain, or swelling) and generally did not necessitate drug discontinuation. Injection site
642 reactions generally occurred in the first month and subsequently decreased in frequency. The mean
643 duration of injection site reactions was 3 to 5 days. Seven percent of patients experienced redness
644 at a previous injection site when subsequent injections were given. In post-marketing experience,
645 injection site bleeding and bruising have also been observed in conjunction with ENBREL[®]
646 therapy.

647 **Infections**

648 In controlled trials, there were no differences in rates of infection among RA, psoriatic arthritis,
649 ankylosing spondylitis, and plaque psoriasis patients treated with ENBREL[®] and those treated with
650 placebo (or MTX for RA and psoriatic arthritis patients). The most common type of infection was
651 upper respiratory infection, which occurred at a rate of approximately 20% among both ENBREL[®]-
652 and placebo-treated patients in RA, psoriatic arthritis, and AS trials, and at a rate of approximately
653 12% among both ENBREL[®]- and placebo-treated patients in plaque psoriasis trials in the first 3
654 months of treatment.

655 In placebo-controlled trials in RA, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis
656 no increase in the incidence of serious infections was observed (approximately 1% in both placebo-
657 and ENBREL[®]-treated groups). In all clinical trials in RA, serious infections experienced by
658 patients have included: pyelonephritis, bronchitis, septic arthritis, abdominal abscess, cellulitis,
659 osteomyelitis, wound infection, pneumonia, foot abscess, leg ulcer, diarrhea, sinusitis, and sepsis.
660 The rate of serious infections has not increased in open-label extension trials and is similar to that
661 observed in ENBREL[®]- and placebo-treated patients from controlled trials. Serious infections,
662 including sepsis and death, have also been reported during post-marketing use of ENBREL[®]. Some
663 have occurred within a few weeks after initiating treatment with ENBREL[®]. Many of the patients
664 had underlying conditions (e.g., diabetes, congestive heart failure, history of active or chronic
665 infections) in addition to their rheumatoid arthritis (see **WARNINGS**). Data from a sepsis clinical
666 trial not specifically in patients with RA suggest that ENBREL[®] treatment may increase mortality
667 in patients with established sepsis.⁹

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

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

676 In clinical trials in plaque psoriasis, serious infections experienced by ENBREL[®]-treated patients
677 have included: cellulitis, gastroenteritis, pneumonia, abscess, and osteomyelitis.

678 **Malignancies**

679 Patients have been observed in clinical trials with ENBREL[®] for over five years. Among 4462
680 rheumatoid arthritis patients treated with ENBREL[®] in clinical trials for a mean of 27 months
681 (approximately 10000 patient-years of therapy), 9 lymphomas were observed for a rate of 0.09
682 cases per 100 patient-years. This is 3-fold higher than the rate of lymphomas expected in the
683 general population based on the Surveillance, Epidemiology, and End Results Database.¹⁰ An
684 increased rate of lymphoma up to several fold has been reported in the rheumatoid arthritis patient
685 population, and may be further increased in patients with more severe disease activity^{11, 12} (see
686 **WARNINGS: Malignancies**). Sixty-seven malignancies, other than lymphoma, were observed.
687 Of these, the most common malignancies were colon, breast, lung and prostate, which were similar
688 in type and number to what would be expected in the general population.¹⁰ Analysis of the cancer
689 rates at 6 month intervals suggest constant rates over five years of observation.

690 In the placebo-controlled portions of the psoriasis studies, 8 of 933 patients who received
691 ENBREL[®] at any dose were diagnosed with a malignancy compared to 1 of 414 patients who
692 received placebo. Among the 1261 patients with psoriasis who received ENBREL[®] at any dose in
693 the controlled and uncontrolled portions of the psoriasis studies (1062 patient-years), a total of 22
694 patients were diagnosed with 23 malignancies; 9 patients with non-cutaneous solid tumors, 12
695 patients with 13 non-melanoma skin cancers (8 basal, 5 squamous), and 1 patient with non-
696 Hodgkin's lymphoma. Among the placebo treated patients (90 patient-years of observation) 1
697 patient was diagnosed with 2 squamous cell cancers. The size of the placebo group and limited
698 duration of the controlled portions of studies precludes the ability to draw firm conclusions.

699 **Immunogenicity**

700 Patients with RA, psoriatic arthritis, ankylosing spondylitis, or plaque psoriasis were tested at
701 multiple timepoints for antibodies to ENBREL[®]. Antibodies to the TNF receptor portion or other
702 protein components of the ENBREL[®] drug product were detected at least once in sera of
703 approximately 6% of adult patients with RA, psoriatic arthritis, ankylosing spondylitis or plaque
704 psoriasis. These antibodies were all non-neutralizing. No apparent correlation of antibody
705 development to clinical response or adverse events was observed. Results from JRA patients were
706 similar to those seen in adult RA patients treated with ENBREL[®]. The long-term immunogenicity
707 of ENBREL[®] is unknown.

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

714

715

716 **Autoantibodies**

717 Patients with RA had serum samples tested for autoantibodies at multiple timepoints. In RA
718 Studies I and II, the percentage of patients evaluated for antinuclear antibodies (ANA) who
719 developed new positive ANA (titer \geq 1:40) was higher in patients treated with ENBREL[®] (11%)
720 than in placebo-treated patients (5%). The percentage of patients who developed new positive
721 anti-double-stranded DNA antibodies was also higher by radioimmunoassay (15% of patients
722 treated with ENBREL[®] compared to 4% of placebo-treated patients) and by *Crithidia luciliae* assay
723 (3% of patients treated with ENBREL[®] compared to none of placebo-treated patients). The
724 proportion of patients treated with ENBREL[®] who developed anticardiolipin antibodies was
725 similarly increased compared to placebo-treated patients. In Study III, no pattern of increased
726 autoantibody development was seen in ENBREL[®] patients compared to MTX patients.

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

731 **Other Adverse Reactions**

732 Table 10 summarizes events reported in at least 3% of all patients with higher incidence in patients
733 treated with ENBREL[®] compared to controls in placebo-controlled RA trials (including the
734 combination methotrexate trial) and relevant events from Study III. In placebo-controlled plaque
735 psoriasis trials, the percentages of patients reporting injection site reactions were lower in the
736 placebo dose group (6.4%) than in the ENBREL[®] dose groups (15.5%) in Studies I and II.
737 Otherwise, the percentages of patients reporting adverse events in the 50 mg twice a week dose
738 group were similar to those observed in the 25 mg twice a week dose group or placebo group. In
739 psoriasis Study I, there were no serious adverse events of worsening psoriasis following withdrawal
740 of study drug. However, adverse events of worsening psoriasis including three serious adverse
741 events were observed during the course of the clinical trials. Urticaria and non-infectious hepatitis
742 were observed in a small number of patients and angioedema was observed in one patient in clinical
743 studies. Urticaria and angioedema have also been reported in spontaneous post-marketing reports.
744 Adverse events in psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis trials were similar
745 to those reported in RA clinical trials.

**Table 10:
Percent of RA Patients Reporting Adverse Events
in Controlled Clinical Trials***

Event	Placebo Controlled		Active Controlled (Study III)	
	Percent of patients		Percent of patients	
	Placebo [†] (N = 152)	ENBREL [®] (N = 349)	MTX (N = 217)	ENBREL [®] (N = 415)
Injection site reaction	10	37	7	34
Infection (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).

747 In controlled trials of RA and psoriatic arthritis, rates of serious adverse events were seen at a
748 frequency of approximately 5% among ENBREL[®] - and control-treated patients. In controlled trials
749 of plaque psoriasis, rates of serious adverse events were seen at a frequency of < 1.5% among
750 ENBREL[®] - and placebo-treated patients in the first 3 months of treatment. Among patients with
751 RA in placebo-controlled, active-controlled, and open-label trials of ENBREL[®], malignancies (see
752 **WARNINGS: Malignancies, ADVERSE REACTIONS: Malignancies**) and infections (see
753 **ADVERSE REACTIONS: Infections**) were the most common serious adverse events observed.
754 Other infrequent serious adverse events observed in RA, psoriatic arthritis, ankylosing spondylitis,
755 or plaque psoriasis clinical trials are listed by body system below:

756	Cardiovascular:	heart failure, myocardial infarction, myocardial ischemia,
757		hypertension, hypotension, deep vein thrombosis,
758		thrombophlebitis
759	Digestive:	cholecystitis, pancreatitis, gastrointestinal hemorrhage,
760		appendicitis
761	Hematologic/Lymphatic:	lymphadenopathy
762	Musculoskeletal:	bursitis, polymyositis
763	Nervous:	cerebral ischemia, depression, multiple sclerosis (see
764		WARNINGS: Neurologic Events)
765	Respiratory:	dyspnea, pulmonary embolism, sarcoidosis
766	Skin:	worsening psoriasis
767	Urogenital:	membranous glomerulonephropathy, kidney calculus

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

772 **Adverse Reactions in Patients with JRA**

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

776 Severe adverse reactions reported in 69 JRA patients ages 4 to 17 years included varicella (see also
777 **PRECAUTIONS: Immunizations**), gastroenteritis, depression/personality disorder, cutaneous
778 ulcer, esophagitis/gastritis, group A streptococcal septic shock, Type 1 diabetes mellitus, and soft
779 tissue and post-operative wound infection.

780 Forty-three of 69 (62%) children with JRA experienced an infection while receiving ENBREL[®]
781 during three months of study (part 1 open-label), and the frequency and severity of infections was
782 similar in 58 patients completing 12 months of open-label extension therapy. The types of
783 infections reported in JRA patients were generally mild and consistent with those commonly seen
784 in outpatient pediatric populations. Two JRA patients developed varicella infection and signs and
785 symptoms of aseptic meningitis which resolved without sequelae.

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

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

796 **Patients with Heart Failure**

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

805 **Adverse Reaction Information from Spontaneous Reports**

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

809 Additional adverse events are listed by body system below:

810	Body as a whole:	angioedema, fatigue, fever, flu syndrome, generalized pain,
811		weight gain
812	Cardiovascular:	chest pain, vasodilation (flushing), new-onset congestive heart
813		failure (see PRECAUTIONS: Patients with Heart Failure)
814	Digestive:	altered sense of taste, anorexia, diarrhea, dry mouth, intestinal
815		perforation
816	Hematologic/Lymphatic:	adenopathy, anemia, aplastic anemia, leukopenia, neutropenia,
817		pancytopenia, thrombocytopenia (see WARNINGS)

818	Musculoskeletal:	joint pain, lupus-like syndrome with manifestations including
819		rash consistent with subacute or discoid lupus
820	Nervous:	paresthesias, stroke, seizures and central nervous system
821		events suggestive of multiple sclerosis or isolated
822		demyelinating conditions such as transverse myelitis or optic
823		neuritis (see WARNINGS)
824	Ocular:	dry eyes, ocular inflammation
825	Respiratory:	dyspnea, interstitial lung disease, pulmonary disease,
826		worsening of prior lung disorder
827	Skin:	cutaneous vasculitis, pruritis, subcutaneous nodules, urticaria

828 **OVERDOSAGE**

829 The maximum tolerated dose of ENBREL[®] has not been established in humans. Toxicology
830 studies have been performed in monkeys at doses up to 30 times the human dose with no evidence
831 of dose-limiting toxicities. No dose-limiting toxicities have been observed during clinical trials of
832 ENBREL[®]. Single IV doses up to 60 mg/m² have been administered to healthy volunteers in an
833 endotoxemia study without evidence of dose-limiting toxicities.

834 **DOSAGE AND ADMINISTRATION**

835 **Adult RA, AS, and Psoriatic Arthritis Patients**

836 The recommended dose of ENBREL[®] for adult patients with rheumatoid arthritis, psoriatic
837 arthritis, or ankylosing spondylitis is 50 mg per week given as one subcutaneous (SC) injection
838 using a 50 mg/mL single-use prefilled syringe. Methotrexate, glucocorticoids, salicylates,
839 nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics may be continued during treatment
840 with ENBREL[®]. Based on a study of 50 mg ENBREL[®] twice weekly in patients with RA that
841 suggested higher incidence of adverse reactions but similar ACR response rates, doses higher than
842 50 mg per week are not recommended (see **ADVERSE REACTIONS**).

843 **Adult Plaque Psoriasis Patients**

844 The recommended starting dose of ENBREL[®] for adult patients is a 50 mg dose given twice weekly
845 (administered 3 or 4 days apart) for 3 months followed by a reduction to a maintenance dose of
846 50 mg per week (see **CLINICAL STUDIES**). The recommended dose should be administered
847 subcutaneously, using 50 mg/mL single-use prefilled syringes.

848 Starting doses of ENBREL[®] of 25 mg or 50 mg per week were also shown to be efficacious. The
849 proportion of responders were related to ENBREL[®] dosage (see **CLINICAL STUDIES**).

850 **JRA Patients**

851 The recommended dose of ENBREL[®] for pediatric patients ages 4 to 17 years with active
852 polyarticular-course JRA is 0.8 mg/kg per week (up to a maximum of 50 mg per week). For
853 pediatric patients weighing 63 kg (138 pounds) or more, the weekly dose of 50 mg may be

854 administered using the prefilled syringe. For pediatric patients weighing 31 to 62 kg (68 to 136
855 pounds), the total weekly dose should be administered as two subcutaneous (SC) injections, either
856 on the same day or 3 or 4 days apart using the multiple-use vial. The dose for pediatric patients
857 weighing less than 31 kg (68 pounds) should be administered as a single SC injection once weekly
858 using the correct volume from the multiple-use vial. Glucocorticoids, nonsteroidal
859 anti-inflammatory drugs (NSAIDs), or analgesics may be continued during treatment with
860 ENBREL[®]. Concurrent use with methotrexate and higher doses of ENBREL[®] have not been
861 studied in pediatric patients.

862 **Preparation of ENBREL[®]**

863 ENBREL[®] is intended for use under the guidance and supervision of a physician. Patients may
864 self-inject when deemed appropriate and if they receive medical follow-up, as necessary. Patients
865 should not self-administer until they receive proper training in how to prepare and administer the
866 correct dose.

867 The ENBREL[®] (etanercept) “Patient Information” insert contains more detailed instructions on the
868 preparation of ENBREL[®].

869 **Preparation of ENBREL[®] Using the Single-use Prefilled Syringe:**

870 Before injection, ENBREL[®] single-use prefilled syringe may be allowed to reach room temperature
871 (approximately 15 to 30 minutes). DO NOT remove the needle cover while allowing the prefilled
872 syringe to reach room temperature.

873 **Preparation of ENBREL[®] Using the Multiple-use Vial:**

874 ENBREL[®] should be reconstituted aseptically with 1 mL of the supplied Sterile Bacteriostatic
875 Water for Injection, USP (0.9% benzyl alcohol) giving a solution of 1.0 mL containing 25 mg of
876 ENBREL[®].

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

883 If using the vial adapter, twist the vial adapter onto the diluent syringe. Then, place the vial adapter
884 over the ENBREL[®] vial and insert the vial adapter into the vial stopper. Push down on the plunger
885 to inject the diluent into the ENBREL[®] vial. It is normal for some foaming to occur. Keeping the
886 diluent syringe in place, gently swirl the contents of the ENBREL[®] vial during dissolution. To
887 avoid excessive foaming, do not shake or vigorously agitate.

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

892 Generally, dissolution of ENBREL[®] takes less than 10 minutes. Visually inspect the solution for
893 particulate matter and discoloration prior to administration. The solution should not be used if
894 discolored or cloudy, or if particulate matter remains.

895 Withdraw the correct dose of reconstituted solution into the syringe. Some foam or bubbles may
896 remain in the vial. Remove the syringe from the vial adapter or remove the 25-gauge needle from
897 the syringe. Attach a 27-gauge needle to inject ENBREL[®].

898 The contents of one vial of ENBREL[®] solution should not be mixed with, or transferred into, the
899 contents of another vial of ENBREL[®]. No other medications should be added to solutions
900 containing ENBREL[®], and do not reconstitute ENBREL[®] with other diluents. Do not filter
901 reconstituted solution during preparation or administration.

902 Reconstitution with the supplied BWFI, using a 25-gauge needle, yields a preserved, multiple-use
903 solution that must be used within 14 days. Discard reconstituted solution after 14 days.

904 **PRODUCT STABILITY AND STERILITY CANNOT BE ASSURED AFTER 14 DAYS.**

905 **Administration of ENBREL[®]**

906 A 50 mg dose should be given as one SC injection using a 50 mg/mL single-use prefilled syringe or
907 as two 25 mg SC injections using the multiple-use vial. The two 25 mg injections should be given
908 either on the same day or 3 or 4 days apart (see **CLINICAL STUDIES**).

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

912 **Storage and Stability**

913 ENBREL[®] single-use prefilled syringe: Do not use a prefilled syringe beyond the expiration date
914 stamped on the carton or syringe barrel label. The prefilled syringes must be refrigerated at 2° to
915 8°C (36° to 46°F). **DO NOT FREEZE.** Keep the ENBREL[®] prefilled syringes in the original
916 carton to protect from light until the time of use. Do not shake.

917 ENBREL[®] multiple-use vial: Do not use a dose tray beyond the expiration date stamped on the
918 carton, dose tray label, vial label, or diluent syringe label. The dose tray containing ENBREL[®]
919 (sterile powder) must be refrigerated at 2° to 8°C (36° to 46°F). **DO NOT FREEZE.**

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

924 **HOW SUPPLIED**

925 ENBREL[®] single-use prefilled syringe is supplied in a carton containing four prefilled syringes
926 (NDC 58406-435-04). Each prefilled syringe contains 0.98 mL of 50 mg/mL of etanercept in a
927 single-use syringe with a 27 gauge, ½-inch needle. Administration of one 50 mg/mL prefilled

928 syringe of ENBREL[®] provides a dose equivalent to two 25 mg vials of lyophilized ENBREL[®],
929 when vials are reconstituted and administered as recommended.

930 ENBREL[®] multiple-use vial is supplied in a carton containing four dose trays (NDC
931 58406-425-34). Each dose tray contains one 25 mg vial of etanercept, one diluent syringe (1 mL
932 Sterile Bacteriostatic Water for Injection, USP, containing 0.9% benzyl alcohol), one 27-gauge
933 ½-inch needle, one vial adapter, one plunger, and two alcohol swabs. Each carton contains four
934 “Mixing Date:” stickers.

935 **Rx Only**

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