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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, $1.2 \pm$
65 0.7 mg/L, and 297 ± 166 mg \cdot 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 \cdot 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.

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82 CLINICAL STUDIES

83 Adult Rheumatoid Arthritis

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

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

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

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

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

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122 **Clinical Response**

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

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
<u>ACR 20</u>						
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%
<u>ACR 50</u>						
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%
<u>ACR 70</u>						
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.

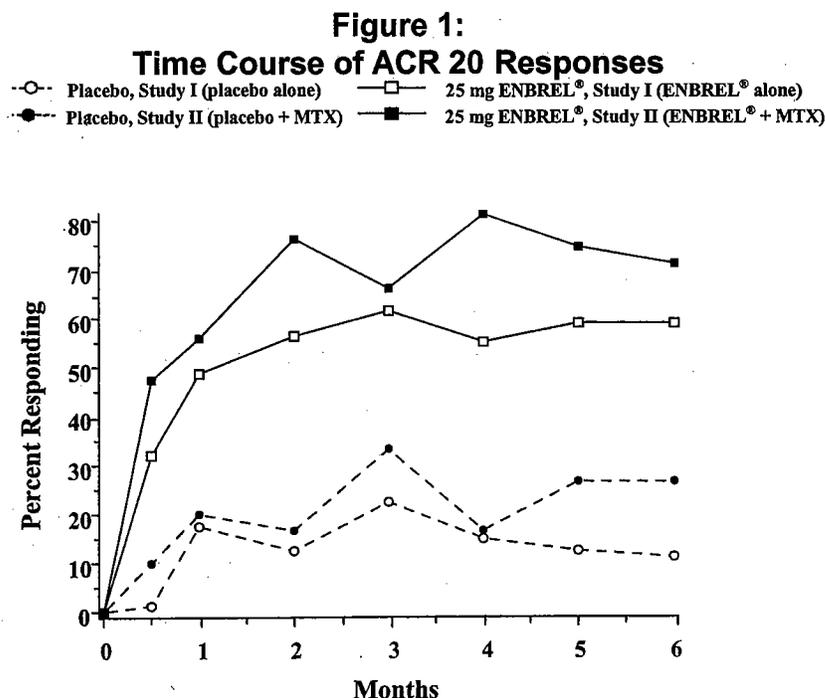
^d Major clinical response is achieving an ACR 70 response for a continuous 6-month period.

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

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

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

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

148

**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.

149

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

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

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

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168 **Physical Function Response**

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

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

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

191 **Radiographic Response**

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

198

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[®]

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

203 In the open-label extension of Study III, 48% of the original patients treated with 25 mg ENBREL[®]
 204 have been evaluated radiographically at 5 years. Patients had continued inhibition of structural
 205 damage, as measured by the TSS, and 55% of them had no progression of structural damage.
 206 Patients originally treated with MTX had further reduction in radiographic progression once they
 207 began treatment with ENBREL[®].

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

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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[®]

215

216 **Once Weekly Dosing**

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

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

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

236 In part 1 of the study, 51 of 69 (74%) patients demonstrated a clinical response and entered part 2.
237 In part 2, 6 of 25 (24%) patients remaining on ENBREL[®] experienced a disease flare compared to
238 20 of 26 (77%) patients receiving placebo ($p = 0.007$). From the start of part 2, the median time to
239 flare was ≥ 116 days for patients who received ENBREL[®] and 28 days for patients who received
240 placebo. Each component of the JRA core set criteria worsened in the arm that received placebo
241 and remained stable or improved in the arm that continued on ENBREL[®]. The data suggested the
242 possibility of a higher flare rate among those patients with a higher baseline ESR. Of patients who
243 demonstrated a clinical response at 90 days and entered part 2 of the study, some of the patients
244 remaining on ENBREL[®] continued to improve from month 3 through month 7, while those who
245 received placebo did not improve.

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

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

253

254 **Psoriatic Arthritis**

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

268 Compared to placebo, treatment with ENBREL[®] resulted in significant improvements in measures
 269 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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272 Among patients with psoriatic arthritis who received ENBREL[®], the clinical responses were
 273 apparent at the time of the first visit (4 weeks) and were maintained through 6 months of therapy.
 274 Responses were similar in patients who were or were not receiving concomitant methotrexate
 275 therapy at baseline. At 6 months, the ACR 20/50/70 responses were achieved by 50%, 37%, and
 276 9%, respectively, of patients receiving ENBREL[®], compared to 13%, 4%, and 1%, respectively, of
 277 patients receiving placebo. Similar responses were seen in patients with each of the subtypes of
 278 psoriatic arthritis, although few patients were enrolled with the arthritis mutilans and ankylosing
 279 spondylitis-like subtypes. The results of this study were similar to those seen in an earlier
 280 single-center, randomized, placebo-controlled study of 60 patients with psoriatic arthritis.

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

287 ***Radiographic Response***

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

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

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310 ***Physical Function Response***

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

320 **Ankylosing Spondylitis**

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

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

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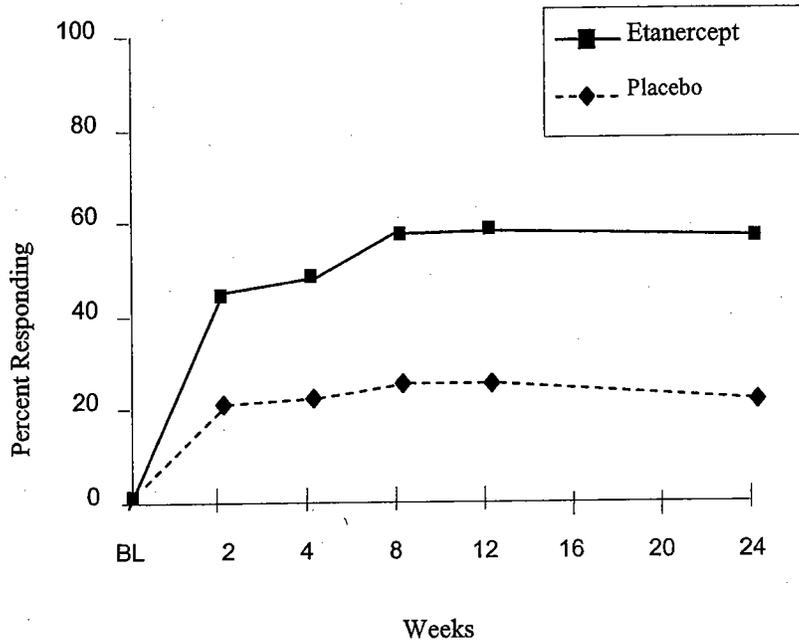
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Figure 2: ASAS 20 Responses in Ankylosing Spondylitis



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

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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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367 **Plaque Psoriasis**

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

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

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

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

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

395 Patients in all treatment groups and in both studies had a median baseline PASI score ranging from
396 15 to 17; and the percentage of patients with baseline sPGA classifications ranged from 54% to
397 66% for moderate, 17% to 26% for marked, and 1% to 5% for severe. Across all treatment groups,
398 the percentage of patients who previously received systemic therapy for psoriasis ranged from 61%
399 to 65% in Study I, and 71% to 75% in Study II; and those who previously received phototherapy
400 ranged from 44% to 50% in Study I, and 72% to 73% in Study II.

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

406
407**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 placebo408
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410**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 placebo411
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Among PASI 75 achievers in both studies, the median time to PASI 50 and PASI 75 was approximately 1 and approximately 2 months, respectively, after the start of therapy with either 25 or 50 mg twice a week.

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

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

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

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

427 **INDICATIONS AND USAGE**

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

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

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

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

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

443 **CONTRAINDICATIONS**

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

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451 **WARNINGS**452 **INFECTIONS**

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

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

477 **Neurologic Events**

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

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491 Hematologic Events

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

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

503 Malignancies

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

515 In a randomized, placebo-controlled study of 180 patients with Wegener's granulomatosis where
 516 ENBREL® was added to standard treatment (including cyclophosphamide, methotrexate, and
 517 corticosteroids), patients receiving ENBREL® experienced more non-cutaneous solid malignancies
 518 than patients receiving placebo (see **ADVERSE REACTIONS: Malignancies**). The addition of
 519 ENBREL® to standard treatment was not associated with improved clinical outcomes when
 520 compared with standard therapy alone. The use of ENBREL® in patients with Wegener's
 521 granulomatosis receiving immunosuppressive agents is not recommended. The use of ENBREL®
 522 in patients receiving concurrent cyclophosphamide therapy is not recommended.

523 PRECAUTIONS

524 General

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

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

530 Information for Patients

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

542 Patients with Heart Failure

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

554 Immunosuppression

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

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567 Immunizations

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

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

579 **Autoimmunity**

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

586 **Drug Interactions**

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

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

594 In a study of patients with Wegener's granulomatosis, the addition of ENBREL[®] to standard
595 therapy (including cyclophosphamide) was associated with a higher incidence of non-cutaneous
596 solid malignancies. The use of ENBREL[®] in patients receiving concurrent cyclophosphamide
597 therapy is not recommended (see **WARNINGS: Malignancies** and **ADVERSE REACTIONS:**
598 **Malignancies**).

599 Patients in a clinical study who were on established therapy with sulfasalazine, to which ENBREL[®]
600 was added, were noted to develop a mild decrease in mean neutrophil counts in comparison to
601 groups treated with either ENBREL[®] or sulfasalazine alone. The clinical significance of this
602 observation is unknown.

603

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

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

608 **Pregnancy (Category B)**

609 Developmental toxicity studies have been performed in rats and rabbits at doses ranging from 60- to
610 100-fold higher than the human dose and have revealed no evidence of harm to the fetus due to
611 ENBREL[®]. There are, however, no studies in pregnant women. Because animal reproduction
612 studies are not always predictive of human response, this drug should be used during pregnancy
613 only if clearly needed.

614 **Pregnancy Registry:** To monitor outcomes of pregnant women exposed to ENBREL[®], a pregnancy
615 registry has been established. Physicians are encouraged to register patients by calling 1-877-311-
616 8972.

617 **Nursing Mothers**

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

622 **Geriatric Use**

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

627 **Pediatric Use**

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

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

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638 **ADVERSE REACTIONS**

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

641 ENBREL[®] has been studied in 1442 patients with RA, followed for up to 80 months, in 169
 642 patients with psoriatic arthritis for up to 24 months, in 222 patients with ankylosing spondylitis for
 643 up to 10 months, and 1261 patients with plaque psoriasis for up to 15 months. In controlled trials,
 644 the proportion of ENBREL[®]-treated patients who discontinued treatment due to adverse events was
 645 approximately 4% in the indications studied. The vast majority of these patients were treated with
 646 25 mg SC twice weekly. In plaque psoriasis studies, ENBREL[®] doses studied were 25 mg SC once
 647 a week, 25 mg SC twice a week, and 50 mg SC twice a week.

648

649 **Injection Site Reactions**

650 In controlled trials in rheumatologic indications, approximately 37% of patients treated with
 651 ENBREL[®] developed injection site reactions. In controlled trials in patients with plaque psoriasis,
 652 14% of patients treated with ENBREL[®] developed injection site reactions during the first 3 months
 653 of treatment. All injection site reactions were described as mild to moderate (erythema and/or
 654 itching, pain, or swelling) and generally did not necessitate drug discontinuation. Injection site
 655 reactions generally occurred in the first month and subsequently decreased in frequency. The mean
 656 duration of injection site reactions was 3 to 5 days. Seven percent of patients experienced redness
 657 at a previous injection site when subsequent injections were given. In post-marketing experience,
 658 injection site bleeding and bruising have also been observed in conjunction with ENBREL[®]
 659 therapy.

660 **Infections**

661 In controlled trials, there were no differences in rates of infection among RA, psoriatic arthritis,
 662 ankylosing spondylitis, and plaque psoriasis patients treated with ENBREL[®] and those treated with
 663 placebo (or MTX for RA and psoriatic arthritis patients). The most common type of infection was
 664 upper respiratory infection, which occurred at a rate of approximately 20% among both ENBREL[®]-
 665 and placebo-treated patients in RA, psoriatic arthritis, and AS trials, and at a rate of approximately
 666 12% among both ENBREL[®]- and placebo-treated patients in plaque psoriasis trials in the first 3
 667 months of treatment.

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

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

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

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

691 **Malignancies**

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

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

712 Among 89 patients with Wegener's granulomatosis receiving ENBREL[®] in a randomized, placebo-
713 controlled trial, 5 experienced a variety of non-cutaneous solid malignancies compared with none
714 receiving placebo (see **WARNINGS: Malignancies**).

715 **Immunogenicity**

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

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

730

731 **Autoantibodies**

732 Patients with RA had serum samples tested for autoantibodies at multiple timepoints. In RA
733 Studies I and II, the percentage of patients evaluated for antinuclear antibodies (ANA) who
734 developed new positive ANA (titer \geq 1:40) was higher in patients treated with ENBREL[®] (11%)
735 than in placebo-treated patients (5%). The percentage of patients who developed new positive
736 anti-double-stranded DNA antibodies was also higher by radioimmunoassay (15% of patients
737 treated with ENBREL[®] compared to 4% of placebo-treated patients) and by *Crithidia luciliae* assay
738 (3% of patients treated with ENBREL[®] compared to none of placebo-treated patients). The
739 proportion of patients treated with ENBREL[®] who developed anticardiolipin antibodies was
740 similarly increased compared to placebo-treated patients. In Study III, no pattern of increased
741 autoantibody development was seen in ENBREL[®] patients compared to MTX patients.

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

746

747 **Other Adverse Reactions**

748 Table 10 summarizes events reported in at least 3% of all patients with higher incidence in patients
749 treated with ENBREL[®] compared to controls in placebo-controlled RA trials (including the
750 combination methotrexate trial) and relevant events from Study III. In placebo-controlled plaque
751 psoriasis trials, the percentages of patients reporting injection site reactions were lower in the
752 placebo dose group (6.4%) than in the ENBREL[®] dose groups (15.5%) in Studies I and II.
753 Otherwise, the percentages of patients reporting adverse events in the 50 mg twice a week dose
754 group were similar to those observed in the 25 mg twice a week dose group or placebo group. In
755 psoriasis Study I, there were no serious adverse events of worsening psoriasis following withdrawal
756 of study drug. However, adverse events of worsening psoriasis including three serious adverse
757 events were observed during the course of the clinical trials. Urticaria and non-infectious hepatitis
758 were observed in a small number of patients and angioedema was observed in one patient in clinical
759 studies. Urticaria and angioedema have also been reported in spontaneous post-marketing reports.
760 Adverse events in psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis trials were similar
761 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).

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

772	Cardiovascular:	heart failure, myocardial infarction, myocardial ischemia,
773		hypertension, hypotension, deep vein thrombosis,
774		thrombophlebitis
775	Digestive:	cholecystitis, pancreatitis, gastrointestinal hemorrhage,
776		appendicitis
777	Hematologic/Lymphatic:	lymphadenopathy
778	Musculoskeletal:	bursitis, polymyositis
779	Nervous:	cerebral ischemia, depression, multiple sclerosis (see
780		WARNINGS: Neurologic Events)
781	Respiratory:	dyspnea, pulmonary embolism, sarcoidosis
782	Skin:	worsening psoriasis
783	Urogenital:	membranous glomerulonephropathy, kidney calculus

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

788 **Adverse Reactions in Patients with JRA**

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

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

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

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

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

812 **Patients with Heart Failure**

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

821 **Adverse Reaction Information from Spontaneous Reports**

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

825 Additional adverse events are listed by body system below:

826	Body as a whole:	angioedema, fatigue, fever, flu syndrome, generalized pain,
827		weight gain
828	Cardiovascular:	chest pain, vasodilation (flushing), new-onset congestive heart
829		failure (see PRECAUTIONS: Patients with Heart Failure)
830	Digestive:	altered sense of taste, anorexia, diarrhea, dry mouth, intestinal
831		perforation
832	Hematologic/Lymphatic:	adenopathy, anemia, aplastic anemia, leukopenia, neutropenia,
833		pancytopenia, thrombocytopenia (see WARNINGS)

834	Musculoskeletal:	joint pain, lupus-like syndrome with manifestations including
835		rash consistent with subacute or discoid lupus
836	Nervous:	paresthesias, stroke, seizures and central nervous system
837		events suggestive of multiple sclerosis or isolated
838		demyelinating conditions such as transverse myelitis or optic
839		neuritis (see WARNINGS)
840	Ocular:	dry eyes, ocular inflammation
841	Respiratory:	dyspnea, interstitial lung disease, pulmonary disease,
842		worsening of prior lung disorder
843	Skin:	cutaneous vasculitis, pruritis, subcutaneous nodules, urticaria

844 **OVERDOSAGE**

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

850 **DOSAGE AND ADMINISTRATION**

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

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

859 **Adult Plaque Psoriasis Patients**

860 The recommended starting dose of ENBREL[®] for adult patients is a 50 mg dose given twice weekly
 861 (administered 3 or 4 days apart) for 3 months followed by a reduction to a maintenance dose of
 862 50 mg per week (see **CLINICAL STUDIES**). The recommended dose should be administered
 863 subcutaneously, using 50 mg/mL single-use prefilled syringes.

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

866 **JRA Patients**

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

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

878 **Preparation of ENBREL[®]**

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

883 The ENBREL[®] (etanercept) "Patient Information" insert contains more detailed instructions on the
884 preparation of ENBREL[®].

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

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

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

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

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

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

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

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

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

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

918 Reconstitution with the supplied BWFI, using a 25-gauge needle, yields a preserved, multiple-use
 919 solution that must be used within 14 days. Discard reconstituted solution after 14 days.
 920 **PRODUCT STABILITY AND STERILITY CANNOT BE ASSURED AFTER 14 DAYS.**

921 Administration of ENBREL[®]

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

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

928 Storage and Stability

929 ENBREL[®] single-use prefilled syringe: Do not use a prefilled syringe beyond the expiration date
 930 stamped on the carton or syringe barrel label. The prefilled syringes must be refrigerated at 2° to
 931 8°C (36° to 46°F). **DO NOT FREEZE**. Keep the ENBREL[®] prefilled syringes in the original
 932 carton to protect from light until the time of use. Do not shake.

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

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

940 HOW SUPPLIED

941 ENBREL[®] single-use prefilled syringe is supplied in a carton containing four prefilled syringes
 942 (NDC 58406-435-04). Each prefilled syringe contains 0.98 mL of 50 mg/mL of etanercept in a
 943 single-dose syringe with a 27 gauge, ½-inch needle. Administration of one 50 mg/mL prefilled
 944 syringe of ENBREL[®] provides a dose equivalent to two 25 mg vials of lyophilized ENBREL[®],
 945 when vials are reconstituted and administered as recommended.

946 ENBREL® multiple-use vial is supplied in a carton containing four dose trays (NDC
 947 58406-425-34). Each dose tray contains one 25 mg vial of etanercept, one diluent syringe (1 mL
 948 Sterile Bacteriostatic Water for Injection, USP, containing 0.9% benzyl alcohol), one 27-gauge
 949 ½-inch needle, one vial adapter, one plunger, and two alcohol swabs. Each carton contains four
 950 "Mixing Date:" stickers.

951 **Rx Only**

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Wyeth®

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989 Immunex Corporation
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ENBREL[®]
(etanercept)
Single-use Prefilled Syringe
PATIENT INFORMATION

ENBREL[®] (pronounced en-brel)

Read these instructions carefully before you start taking ENBREL[®]. You should read this leaflet each time you get your prescription refilled, in case something has changed. The information in this leaflet does not take the place of talking with your doctor before you start taking this medication and at check-ups. Talk to your doctor if you have any questions about your treatment with ENBREL[®].

What is ENBREL[®]?

ENBREL[®] is a medicine for adults and children with moderate to severe forms of rheumatoid arthritis (RA) and a type of disease called psoriatic (sore-ee-ah-tick) arthritis. ENBREL[®] is also for adults with a type of arthritis called ankylosing spondylitis (ank-e-low-sing spond-e-lie-tis) (AS). ENBREL[®] is also for adults with moderate to severe psoriasis (sore-I-ah-sis). RA, psoriatic arthritis, and AS are inflammatory diseases that affect the joints in your body. Psoriasis is an inflammatory disease that affects the skin and can cause raised, thick, red and scaly patches (“psoriatic skin lesions”) that can appear anywhere on the body. Psoriatic arthritis is usually seen in patients with psoriasis and affects both the joints and the skin.

How does ENBREL[®] work?

ENBREL[®] is a type of protein called a tumor necrosis factor (TNF) blocker that blocks the action of a substance your body makes called TNF-alpha. Tumor necrosis factor-alpha is made by your body’s immune system. People with immune diseases like RA, psoriasis, and psoriatic arthritis, as well as patients with AS, have too much TNF-alpha in their bodies, which can cause inflammation and lead to painful, swollen joints and raised, thick, red, scaly patches (“psoriatic skin lesions”) that can appear anywhere on the body. ENBREL[®] can reduce the amount of TNF in the body to normal levels, helping to treat joint damage and skin lesions.

While taking ENBREL[®] can block the damage that too much TNF-alpha can cause, it can also lower the ability of your immune system to fight infections. So, taking ENBREL[®] can make you more prone to getting infections or make any infection that you may have worse.

What important information do I need to know about taking ENBREL®?

All medicines have side effects. Medicines, like ENBREL®, that affect your immune system can cause serious side effects. The possible serious side effects include:

- **Serious infections.** There have been rare cases where patients taking ENBREL® or other TNF-blocking agents have developed serious infections, including tuberculosis (TB) and infections caused by bacteria or fungi that have spread throughout their body (sepsis). Some patients have died from these infections. If you tend to get infections easily or if you develop an infection while taking ENBREL®, you should tell your doctor right away. Taking ENBREL® with Kineret® (anakinra) is not recommended because this may increase your risk of getting a serious infection.
- **Nervous system diseases.** There have been rare cases of disorders that affect the nervous system of people taking ENBREL® or other TNF blockers. Signs that you could be experiencing a problem affecting your nervous system include: numbness or tingling throughout your body, problems with your vision, weakness in your arms and/or legs, and dizziness.
- **Blood problems.** In some patients the body may fail to produce enough of the blood cells that help your body fight infections or help you to stop bleeding. If you develop a fever that doesn't go away, bruise or bleed very easily or look very pale, call your doctor right away. Your doctor may decide to stop your treatment. Some people have also had symptoms that resemble lupus (rash on your face and arms that gets worse in the sun) that may go away when you stop taking ENBREL®.
- **Heart problems.** You should also tell your doctor if you have ever been treated for heart failure. If you have, your doctor may choose not to start you on ENBREL®, or may want to monitor you more closely.
- **Allergic reactions.** Some patients have had allergic reactions to ENBREL®. If you develop a severe rash, swollen face or difficulty breathing while taking ENBREL®, call your doctor right away.
- **Malignancies.** RA patients, particularly those with highly active RA, may be at higher risk for lymphoma (a type of cancer). There have been rare reports of lymphoma in patients taking ENBREL® or other TNF blockers, occurring more often than expected for people in general. The role of ENBREL® in the development of cancer is not known.

Before you start taking ENBREL® you should tell your doctor if you have or have had any of the following:

- Any kind of infection including an infection that is in only one place in your body (such as an open sore), or an infection that is in your whole body (such as the flu). Having an infection could put you at risk for serious side effects from ENBREL®.

- A history of infections that keep coming back or other conditions, like diabetes, that might increase your risk of infections.
- Tuberculosis (TB), or if you have been in close contact with someone who has had tuberculosis. If you develop any of the symptoms of tuberculosis (a dry cough that doesn't go away, weight loss, fever, night sweats) call your doctor. You will need to be examined for TB and have a skin test.
- Any numbness or tingling or a disease that affects your nervous system like multiple sclerosis.
- Been newly diagnosed or are being treated for congestive heart failure.
- Been scheduled to have major surgery.
- Been scheduled to be vaccinated for anything.

If you are not sure or have any questions about any of this information, ask your doctor.

What are the other more common side effects with ENBREL®?

- Reactions where the injection was given. These reactions are usually mild and include redness, rash, swelling, itching, or bruising. These usually go away within 3 to 5 days. If you have pain, redness or swelling around the injection site that doesn't go away or gets worse, call your doctor.
- Upper respiratory infections (sinus infections)
- Headaches

What are other possible side effects with ENBREL®?

- The needle cover on the single-use prefilled syringe contains latex. Tell your doctor if you have any allergies to rubber or latex.

Who should not take ENBREL®?

You should not take ENBREL® if you have ever had an allergic reaction to ENBREL®.

Can I take ENBREL® if I am pregnant or breast-feeding?

ENBREL® has not been studied in pregnant women or nursing mothers, so we don't know what the effects are on pregnant women or nursing babies. You should tell your doctor if you are pregnant, become pregnant, or are thinking about becoming pregnant.

Pregnancy Registry: Amgen has developed a registry for pregnant women exposed to ENBREL®. The purpose of this registry is to check the health of the pregnant mother and her child. Patients are encouraged to contact the registry themselves or ask their doctors to contact the registry for them by calling 1-877-311-8972.

Can I take ENBREL[®] if I am taking other medicines for my Rheumatoid Arthritis, Psoriasis, Psoriatic Arthritis, Ankylosing Spondylitis or other conditions?

Yes, you can take other medicines if your doctor has prescribed them or has told you it is OK to take them while you are taking ENBREL[®]. It is important that you tell your doctor about any other medicines (for example, high blood pressure medicine) you are taking for other conditions before you start taking ENBREL[®]. Taking ENBREL[®] with Kineret[®] (anakinra) is not recommended because this may increase your risk of getting a serious infection. Taking ENBREL[®] with cyclophosphamide (used to treat cancer or other immune diseases) is not recommended.

You should also tell your doctor about any over-the-counter drugs, herbal medicines and vitamin and mineral supplements you are taking.

How do I take ENBREL[®]?

ENBREL[®] is given by injection under the skin.

Make sure you have been shown how to inject ENBREL[®] before you do it yourself. You can call your doctor or the ENBREL[®] toll-free information line at 1-888-4ENBREL (1-888-436-2735) if you have any questions about ENBREL[®] or about giving yourself an injection. Someone you know can also help you with your injection. Remember to take this medicine just as your doctor has told you and do not miss any doses.

Adults

If you have RA, psoriatic arthritis, or AS, the recommended dose of ENBREL[®] for adults is 50 mg per week given as one injection using a single-use prefilled syringe.

If you have psoriasis, the recommended starting dose of ENBREL[®] for adult patients is a 50 mg dose twice a week (3 or 4 days apart) given for three months. After 3 months, your doctor will tell you to reduce your dose to 50 mg once per week. The 50 mg dose of ENBREL[®] can be given as one injection using a single-use prefilled syringe.

Children

The recommended dose of ENBREL[®] for children with juvenile rheumatoid arthritis is based upon the child's body weight. Your child's doctor will tell you the correct amount of ENBREL[®] your child should take. **The 50 mg/mL single-use prefilled syringe of ENBREL[®] is only recommended for children weighing 138 pounds or more.**

What should I do if I miss a dose of ENBREL[®]?

If you forget to take ENBREL[®] when you are supposed to, contact your doctor to find out when to take your next dose of ENBREL[®].

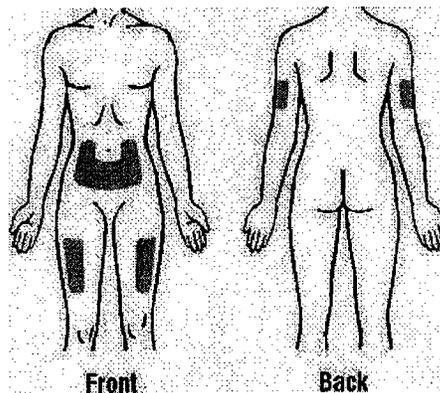
What do I need to do to prepare and give an injection of ENBREL®?

STEP 1: Setting Up for an Injection

1. Select a clean, well-lit, flat work surface, such as a table.
2. Take the ENBREL® carton containing the prefilled syringes out of the refrigerator and place it on your flat work surface. Remove one prefilled syringe and place it on your work surface. Do not shake the prefilled syringe of ENBREL®. Place the carton containing any remaining prefilled syringes back into the refrigerator (2° to 8°C (36° to 46°F)). If you have any questions about storage, contact your doctor, nurse, or pharmacist for further instructions.
3. Check the expiration date on the prefilled syringe. If the expiration date has passed, do not use the prefilled syringe and contact your pharmacist or call 1-888-4ENBREL (1-888-436-2735) for assistance.
4. Wait 15 to 30 minutes to allow the ENBREL® in the prefilled syringe to reach room temperature. DO NOT remove the needle cover while allowing it to reach room temperature. Do not warm ENBREL® in any other way (for example, do not warm it in a microwave or in hot water).
5. Assemble the additional supplies you will need for your injection. These include an alcohol swab, a cotton ball or gauze, and a puncture-resistant disposal container.
6. Wash your hands with soap and warm water.
7. Make sure the solution in the prefilled syringe is clear and colorless. **Do not inject the solution if it is discolored, contains lumps, flakes, or particles.** If the solution in the prefilled syringe is not clear and colorless, or contains particles; contact your pharmacist or call 1-888-4ENBREL (1-888-436-2735) for assistance.

STEP 2: Choosing and Preparing an Injection Site

1. Three recommended injection sites for ENBREL® using a prefilled syringe include: (1) the front of the middle thighs; (2) the abdomen, except for the two-inch area right around the navel; and, (3) the outer area of the upper arms.



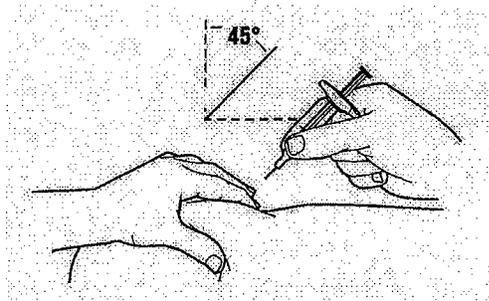
2. Rotate the site for each injection. Do not inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars or stretch marks.
3. If you have psoriasis, you should try not to inject directly into any raised, thick, red, or scaly skin patches (“psoriasis skin lesions”).
4. To prepare the area of skin where ENBREL[®] is to be injected, wipe the injection site with an alcohol swab. **Do not touch this area again before giving the injection.**

STEP 3: Injecting ENBREL[®] Using a Prefilled Syringe

1. Pick up the prefilled syringe from your flat work surface. Hold the barrel of the prefilled syringe with one hand and pull the needle cover straight off.

When you remove the needle cover, there may be a drop of liquid at the end of the needle; this is normal. Do not touch the needle or allow it to touch any surface. Do not touch or bump the plunger. Doing so could cause the liquid to leak out.

2. Holding the syringe with the needle pointing up, check the syringe for air bubbles. If there are bubbles, gently tap the syringe with your finger until the air bubbles rise to the top of the syringe. Slowly push the plunger up to force the air bubbles out of the syringe.
3. Holding the syringe in one hand like a pencil, use the other hand to gently pinch a fold of skin at the cleaned injection site and hold it firmly.
4. Insert the needle at a slight angle (45 degrees) to the skin. With a quick, “dart-like” motion, insert the needle into the skin.



5. After the needle is inserted, let go of the skin. Pull the plunger back slightly. If blood comes into the syringe, do not inject ENBREL[®] because the needle has entered a blood vessel. Withdraw the needle and discard it in a puncture-resistant container. Repeat the steps to prepare for an injection using a new prefilled syringe of ENBREL[®]. Do not use the same prefilled syringe.
6. If no blood appears in the syringe, slowly push the plunger all the way down to inject ENBREL[®].
7. When the syringe is empty, pull the needle out of the skin, being careful to keep it at the same angle as inserted. There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site for 10 seconds. Do not rub the injection site. If needed, you may cover the injection site with a bandage.

STEP 4: Disposing of Supplies

- The syringe should **NEVER** be reused. **NEVER** recap a needle.
- Dispose of the used syringe in a puncture-resistant container. Use a hard plastic container with a screw top or hard plastic lid. A SHARPS container made specifically for disposing of used syringes and needles may be used. Puncture-resistant containers may also be purchased at your local pharmacy. **Do not** recycle the container.
- Keep the container out of reach of children. When the container is about two-thirds full, dispose of it as instructed by your healthcare provider. Follow any special state or local laws regarding the proper disposal of needles and syringes.
- Used alcohol swabs should be placed in the trash.

A healthcare provider familiar with ENBREL[®] should answer all questions. A toll-free information service is also available: 1-888-4ENBREL (1-888-436-2735).



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ENBREL[®]
(etanercept)
Multiple-use Vial
PATIENT INFORMATION

ENBREL[®] (pronounced en-brel)

Read these instructions carefully before you start taking ENBREL[®]. You should read this leaflet each time you get your prescription refilled, in case something has changed. The information in this leaflet does not take the place of talking with your doctor before you start taking this medication and at checkups. Talk to your doctor if you have any questions about your treatment with ENBREL[®].

What is ENBREL[®]?

ENBREL[®] is a medicine for adults and children with moderate to severe forms of rheumatoid arthritis (RA) and a type of disease called psoriatic (sore-ee-ah-tick) arthritis. ENBREL[®] is also for adults with a type of arthritis called ankylosing spondylitis (ank-e-low-sing spond-e-lie-tis) (AS). ENBREL[®] is also for adults with moderate to severe psoriasis (sore-I-ah-sis). RA, psoriatic arthritis, and AS are inflammatory diseases that affect the joints in your body. Psoriasis is an inflammatory disease that affects the skin and can cause raised, thick, red and scaly patches ("psoriatic skin lesions") that can appear anywhere on the body. Psoriatic arthritis is usually seen in patients with psoriasis and affects both the joints and the skin.

How does ENBREL[®] work?

ENBREL[®] is a type of protein called a tumor necrosis factor (TNF) blocker that blocks the action of a substance your body makes called TNF-alpha. Tumor necrosis factor-alpha is made by your body's immune system. People with immune diseases like RA, psoriasis, and psoriatic arthritis, as well as patients with AS, have too much TNF-alpha in their bodies, which can cause inflammation and lead to painful, swollen joints and raised, thick, red, scaly patches ("psoriatic skin lesions") that can appear anywhere on the body. ENBREL[®] can reduce the amount of TNF in the body to normal levels, helping to treat joint damage and skin lesions.

While taking ENBREL[®] can block the damage that too much TNF-alpha can cause, it can also lower the ability of your immune system to fight infections. So, taking ENBREL[®] can make you more prone to getting infections or make any infection that you may have worse.

What important information do I need to know about taking ENBREL®?

All medicines have side effects. Medicines, like ENBREL®, that affect your immune system can cause serious side effects. The possible serious side effects include:

- **Serious infections.** There have been rare cases where patients taking ENBREL® or other TNF-blocking agents have developed serious infections, including tuberculosis (TB) and infections caused by bacteria or fungi that have spread throughout their body (sepsis). Some patients have died from these infections. If you tend to get infections easily or if you develop an infection while taking ENBREL®, you should tell your doctor right away. Taking ENBREL® with Kineret® (anakinra) is not recommended because this may increase your risk of getting a serious infection.
- **Nervous system diseases.** There have been rare cases of disorders that affect the nervous system of people taking ENBREL® or other TNF blockers. Signs that you could be experiencing a problem affecting your nervous system include: numbness or tingling throughout your body, problems with your vision, weakness in your arms and/or legs and dizziness.
- **Blood problems.** In some patients the body may fail to produce enough of the blood cells that help your body fight infections or help you to stop bleeding. If you develop a fever that doesn't go away, bruise or bleed very easily or look very pale, call your doctor right away. Your doctor may decide to stop your treatment. Some people have also had symptoms that resemble lupus (rash on your face and arms that gets worse in the sun) that may go away when you stop taking ENBREL®.
- **Heart problems.** You should also tell your doctor if you have ever been treated for heart failure. If you have, your doctor may choose not to start you on ENBREL®, or may want to monitor you more closely.
- **Allergic reactions.** Some patients have had allergic reactions to ENBREL®. If you develop a severe rash, swollen face or difficulty breathing while taking ENBREL®, call your doctor right away.
- **Malignancies.** RA patients, particularly those with highly active RA, may be at higher risk for lymphoma (a type of cancer). There have been rare reports of lymphoma in patients taking ENBREL® or other TNF blockers, occurring more often than expected for people in general. The role of ENBREL® in the development of cancer is not known.

Before you start taking ENBREL® you should tell your doctor if you have or have had any of the following:

- Any kind of infection including an infection that is in only one place in your body (such as an open sore), or an infection that is in your whole body (such as the flu). Having an infection could put you at risk for serious side effects from ENBREL®.

- A history of infections that keep coming back or other conditions, like diabetes, that might increase your risk of infections.
- Tuberculosis (TB), or if you have been in close contact with someone who has had tuberculosis. If you develop any of the symptoms of tuberculosis (a dry cough that doesn't go away, weight loss, fever, night sweats) call your doctor. You will need to be examined for TB and have a skin test.
- Any numbness or tingling or a disease that affects your nervous system like multiple sclerosis.
- Been newly diagnosed or are being treated for congestive heart failure.
- Been scheduled to have major surgery.
- Been scheduled to be vaccinated for anything.

If you are not sure or have any questions about any of this information, ask your doctor.

What are the other more common side effects with ENBREL®?

- Reactions where the injection was given. These reactions are usually mild and included redness, rash, swelling, itching, or bruising. These usually go away within 3 to 5 days. If you have pain, redness or swelling around the injection site that doesn't go away or gets worse, call your doctor.
- Upper respiratory infections (sinus infections)
- Headaches

Who should not take ENBREL®?

You should not take ENBREL® if you have ever had an allergic reaction to ENBREL®.

Can I take ENBREL® if I am pregnant or breast-feeding?

ENBREL® has not been studied in pregnant women or nursing mothers, so we don't know what the effects are on pregnant women or nursing babies. You should tell your doctor if you are pregnant, become pregnant, or are thinking about becoming pregnant.

Pregnancy Registry: Amgen has developed a registry for pregnant women exposed to ENBREL®. The purpose of this registry is to check the health of the pregnant mother and her child. Patients are encouraged to contact the registry themselves or ask their doctors to contact the registry for them by calling 1-877-311-8972.

Can I take ENBREL® if I am taking other medicines for my Rheumatoid Arthritis, Psoriasis, Psoriatic Arthritis, Ankylosing Spondylitis or other conditions?

A Confidential

Cyclophosphamide Update; 7/28/05

Yes, you can take other medicines if your doctor has prescribed them or has told you it is OK to take them while you are taking ENBREL[®]. It is important that you tell your doctor about any other medicines (for example, high blood pressure medicine) you are taking for other conditions before you start taking ENBREL[®]. Taking ENBREL[®] with Kineret[®] (anakinra) is not recommended because this may increase your risk of getting a serious infection. Taking ENBREL[®] with cyclophosphamide (used to treat cancer or other immune diseases) is not recommended.

You should also tell your doctor about any over-the-counter drugs, herbal medicines and vitamin and mineral supplements you are taking.

How do I take ENBREL[®]?

ENBREL[®] is given by injection under the skin.

If you have RA, psoriatic arthritis, or AS, the recommended dose of ENBREL[®] for adults is 50 mg per week (two 25 mg injections). Your doctor will tell you whether the two injections should be given on the same day once a week or on two different days (3 or 4 days apart) in the same week.

The recommended dose of ENBREL[®] for children is based on the child's body weight. Your child's doctor will tell you the correct amount of ENBREL[®] your child should take and whether the dose should be given as one or two injections. Your child's doctor will also tell you whether the injection or injections should be given on the same day once a week or on two different days (3 or 4 days apart) in the same week.

If you have psoriasis, the recommended starting dose of ENBREL[®] for adult patients is a 50 mg dose twice a week (3 or 4 days apart) given for three months. After 3 months, your doctor will tell you to reduce your dose to 50 mg once per week. The 50 mg dose should be given as two 25 mg injections at two different sites.

Make sure you have been shown how to inject ENBREL[®] before you do it yourself. You can call your doctor or the ENBREL[®] toll-free information line at 1-888-4ENBREL (1-888-436-2735) if you have any questions about ENBREL[®] or about giving yourself or your child an injection. Someone you know can also help you with your injection. Remember to take this medicine just as your doctor has told you and do not miss any doses.

What should I do if I miss a dose of ENBREL[®]?

If you forget to take ENBREL[®] when you are supposed to, contact your doctor to find out when to take your next dose of ENBREL[®].

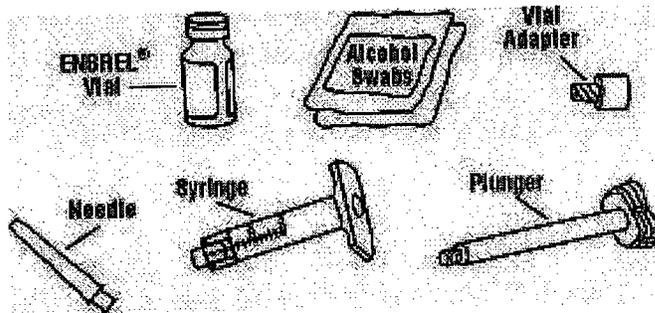
What do I need to do to prepare and give an injection of ENBREL[®]?

STEP 1: Setting up for an Injection

A Confidential

Cyclophosphamide Update; 7/28/05

1. Select a clean, well-lit, flat work surface, such as a table.
2. Take the ENBREL[®] dose tray out of the refrigerator and place it on your flat work surface.
3. Check the expiration date on the dose tray. If the expiration date has passed, do not use the dose tray. Also check to make sure the dose tray has seven items as pictured below:
 - One prefilled diluent syringe containing 1 mL of diluent (liquid) with attached gray tip cap
 - One plunger
 - One ENBREL[®] vial
 - One 27-gauge ½ inch needle in hard plastic cover
 - One vial adapter
 - Two alcohol swabs



If the expiration date has passed, the seven items are not included in the dose tray or if any item looks damaged, contact your pharmacist or call 1-888-4ENBREL (1-888-436-2735) for assistance.

4. Wash your hands with soap and warm water.
5. Peel the paper seal off the dose tray and remove all items.
6. Inspect the volume of diluent in the syringe with the gray tip cap pointing down. Use the unit markings on the side of the syringe to make sure there is at least 1 mL of liquid in the syringe. If the level of liquid is below the 1 mL mark, do not use. Call 1-888-4ENBREL (1-888-436-2735) for assistance.

STEP 2: Preparing the ENBREL[®] Solution

There are two methods for preparing the ENBREL[®] solution. For some children, one vial of ENBREL[®] solution can be used for more than one dose. The free-hand method should

be used for children on ENBREL[®] who are using one vial of ENBREL[®] solution for more than one dose. **You should not use the vial adapter method if you will be using the vial more than once.** Ask your healthcare provider if you have questions about which method to use.

- **The Vial Adapter Method**

Adult patients and larger children on ENBREL[®] may use the vial adapter device to assist with mixing the powder with the liquid and withdrawing ENBREL[®], and then use a 27-gauge needle to inject the dose. **This method should not be used for children using multiple doses from the same vial of ENBREL[®].** The instructions for using the vial adapter method are in STEP 2A.

- **The Free-Hand Method**

In the free-hand method, a 25-gauge needle is used to assist with mixing the powder with the liquid and withdrawing ENBREL[®], and a 27-gauge needle is used to inject the dose. Instructions for using the free-hand method are in STEP 2B.

The instructions for preparing additional doses from the same vial of ENBREL[®] solution are in STEP 3. For each additional dose, you will need two new needles (one 25-gauge needle to withdraw the solution and one 27-gauge needle for injection) and one new empty syringe (1 mL). **NEVER REUSE A SYRINGE OR NEEDLE.**

If you are using the vial of ENBREL[®] for more than one dose, you should write the date you mixed the powder and liquid in the area marked "Mixing Date:" on the supplied sticker attached to these instructions, and attach the sticker to the ENBREL[®] vial.

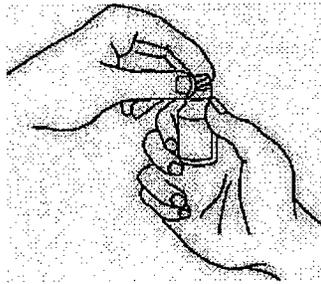
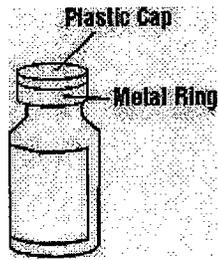
After you have withdrawn the dose of ENBREL[®] that you need, store the ENBREL[®] vial (in the dose tray) in the refrigerator at 36° to 46°F (2° to 8°C) as soon as possible, but always within 4 hours of mixing the solution.

The ENBREL[®] solution must be used within 14 days of the mixing date. You should discard the ENBREL[®] vial and any remaining solution if it is not used within 14 days. Do not mix any remaining liquid in one vial of ENBREL[®] solution with another.

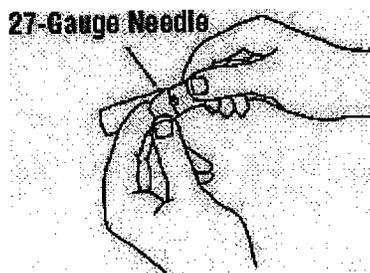
There is a tool available which can help you remove the pink plastic cap on the ENBREL[®] vial, the gray tip cap on the prefilled diluent syringe and the needle cover on the syringe. This cap removal tool is provided to ENBREL[®] patients in the Resource Kit. You can request the Resource Kit by calling 1-888-4ENBREL (1-888-436-2735).

STEP 2A: Vial Adapter Method

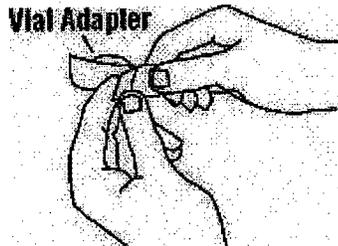
1. Remove the pink plastic cap from the ENBREL[®] vial. Do not remove the gray stopper or silver metal ring around the top of the ENBREL[®] vial.



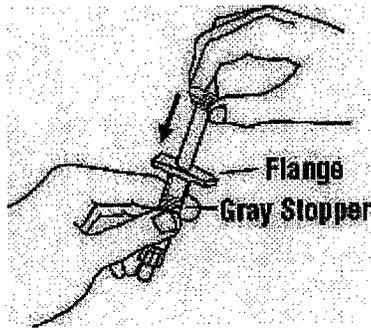
2. Place the ENBREL[®] vial on your flat work surface or turn your dose tray upside down and place your ENBREL[®] vial in the round space marked "V". Use one alcohol swab to clean the gray stopper on the ENBREL[®] vial. Do not touch the gray stopper with your hands.
3. Open the wrapper that contains the 27-gauge needle by peeling apart the tabs and set the needle aside for later use.



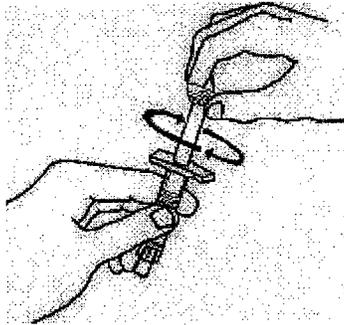
4. Open the wrapper that contains the vial adapter by peeling apart the tabs and set the vial adapter aside for later use. Do not touch the spike inside the vial adapter.



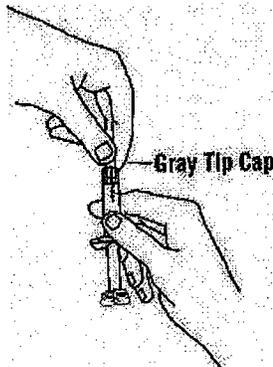
5. Slide the plunger into the flange end of the syringe.



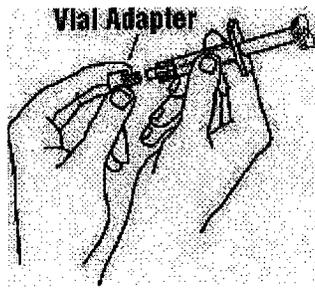
6. Attach the plunger to the gray rubber stopper in the syringe by turning the plunger clockwise until a slight resistance is felt.



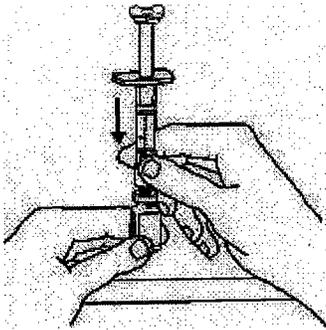
7. Remove the gray tip cap from the prefilled diluent syringe. Do not bump or touch the plunger. Doing so could cause the liquid to leak out. You may see a drop of liquid when removing the gray tip cap. This is normal. Place the gray tip cap on your flat work surface. Do not touch the syringe tip.



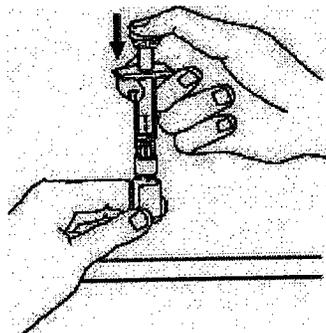
8. Once the gray tip cap is removed, pick up the vial adapter with your free hand. Twist the vial adapter onto the syringe until a slight resistance is felt. Do not over-tighten.



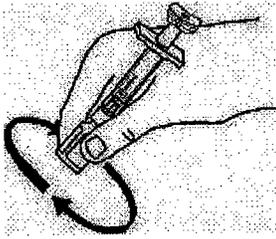
9. Hold the ENBREL[®] vial upright on your flat work surface. Grasp the sides of the vial adapter and place it over the top of the ENBREL[®] vial. Do not bump or touch the plunger. Doing so could cause the liquid to leak out. Insert the vial adapter into the gray stopper on the ENBREL[®] vial. The plastic spike inside the vial adapter should puncture the gray stopper. The vial adapter should fit snugly.



10. Hold the ENBREL[®] vial upright on your flat work surface and push the plunger down until all the liquid from the syringe is in the ENBREL[®] vial. You may see foaming (bubbles) in the vial. This is normal.

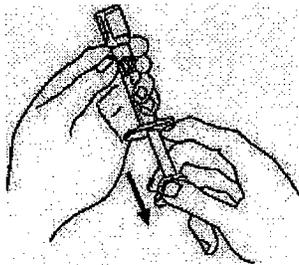


11. Gently swirl the ENBREL[®] vial in a circular motion to dissolve the powder. If you used the dose tray to hold your ENBREL[®] vial, take the vial (with the vial adapter and syringe still attached) out of the dose tray, and gently swirl the vial in a circular motion to dissolve the powder.

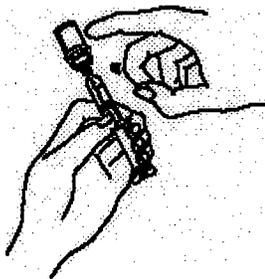


DO NOT SHAKE. Wait until all the powder dissolves (usually less than 10 minutes). The solution should be clear and colorless. After the powder has completely dissolved, foam (bubbles) may still be present. This is normal. **Do not inject the solution if it is discolored, contains lumps, flakes, or particles.** If all the powder in the ENBREL[®] vial is not dissolved or there are particles present after 10 minutes, call 1-888-4ENBREL (1-888-436-2735) for assistance.

12. Turn the ENBREL[®] vial upside down. Hold the syringe at eye level and slowly pull the plunger down to the unit markings on the side of the syringe that correspond with your/your child's dose. For adult patients, remove the entire volume (1 mL), unless otherwise instructed by your doctor. Be careful not to pull the plunger completely out of the syringe. Some white foam may remain in the ENBREL[®] vial. This is normal.

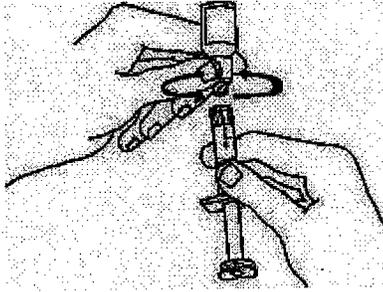


13. Check for air bubbles in the syringe. Gently tap the syringe to make any air bubbles rise to the top of the syringe. Slowly push the plunger up to remove the air bubbles. If you push solution back into the vial, slowly pull back on the plunger to again draw the correct amount of solution back into the syringe.

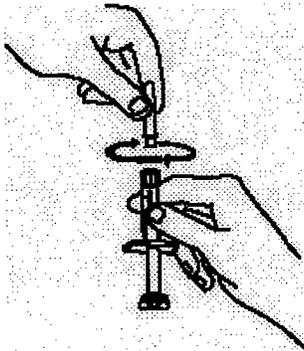


14. Remove the syringe from the vial adapter, by holding the vial adapter with one hand and turning the syringe counterclockwise with your other hand. Do not touch or

bump the plunger. Place the ENBREL[®] vial with the vial adapter on your flat work surface.



15. Continue to hold the barrel of the syringe. With your free hand, twist the 27-gauge needle onto the tip of the syringe until it fits snugly. Do not remove the needle cover from the syringe. Place the syringe on your flat work surface until you are ready to inject ENBREL[®].

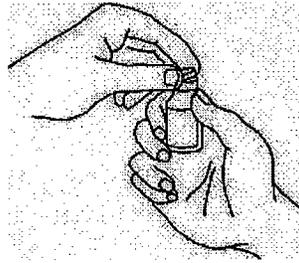


GO TO STEP 4: CHOOSING AND PREPARING AN INJECTION SITE.

STEP 2B: Free-Hand Method

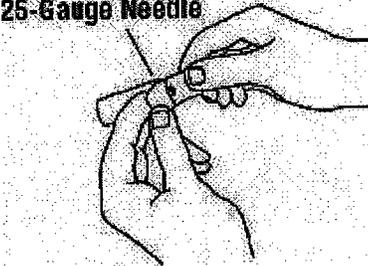
If you are preparing a dose from an ENBREL[®] vial that was previously used, go to STEP 3: Preparing Additional Doses from a Single ENBREL[®] Vial.

1. Remove the pink plastic cap from the ENBREL[®] vial. Do not remove the gray stopper or silver metal ring around the top of the ENBREL[®] vial. Write the date you mix the powder and solution on the supplied "Mixing Date:" sticker and attach it to the ENBREL[®] vial.

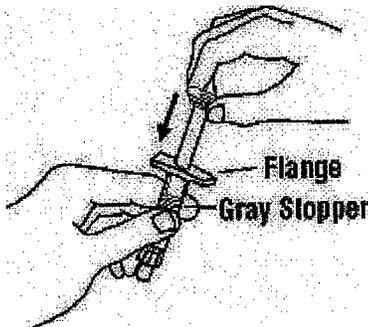


2. Place the ENBREL[®] vial on your flat work surface. Use one alcohol swab to clean the gray stopper on the ENBREL[®] vial. Do not touch the gray stopper with your hands.
3. Open the wrapper that contains the 25-gauge needle by peeling apart the tabs and set the needle aside for later use. The 25-gauge needle will be used to mix the liquid with the powder and for withdrawing ENBREL[®] from the vial.

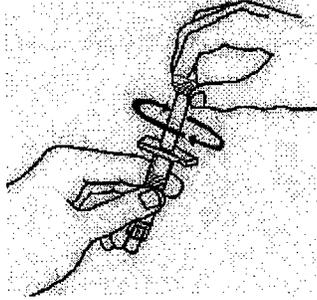
25-Gauge Needle



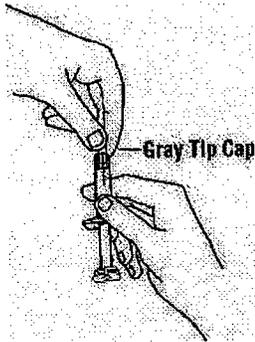
4. Slide the plunger into the flange end of the syringe.



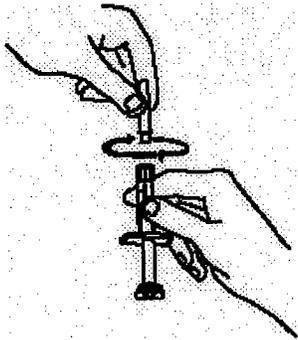
5. Attach the plunger to the gray rubber stopper in the syringe by turning the plunger clockwise until a slight resistance is felt.



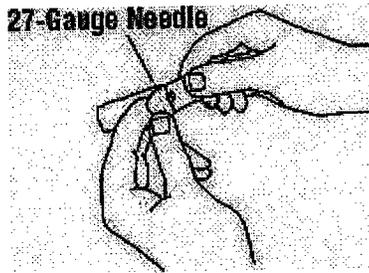
6. Remove the gray tip cap from the prefilled diluent syringe. Do not touch or bump the plunger. Doing so could cause the liquid to leak out. You may see a drop of liquid when removing the tip cap. This is normal. Place the gray tip cap on your flat work surface. Do not touch the syringe tip.



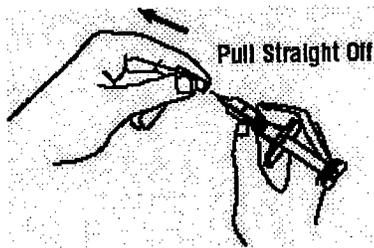
7. Continue to hold the barrel of the syringe. With your free hand, twist the 25-gauge needle onto the tip of the syringe until it fits snugly. Place the syringe on your flat work surface.



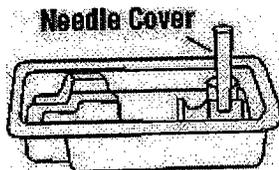
8. Open the wrapper that contains the 27-gauge needle by peeling apart the tabs and set the needle aside for later use. The 27-gauge needle will be used to inject the dose.



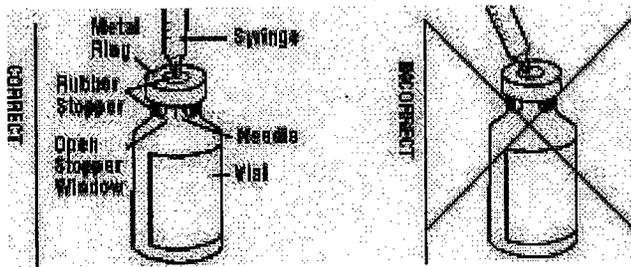
9. Pick up the syringe from your flat work surface. Hold the barrel of the syringe with one hand, and pull the needle cover straight off. Do not touch the needle or allow it to touch any surface. Do not touch or bump the plunger. Doing so could cause the liquid to leak out.



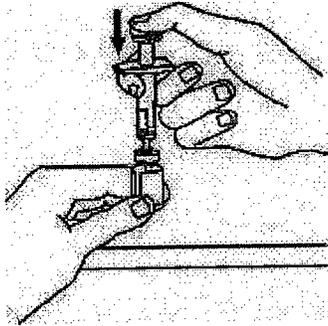
10. Place the needle cover (open side up) in the round space marked "N" in the ENBREL[®] dose tray.



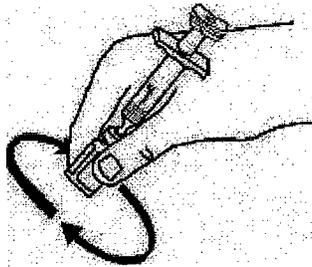
11. Place the ENBREL[®] vial on your flat work surface. Hold the syringe with the needle facing up, and gently pull back on the plunger to pull a small amount of air into the syringe. Then, insert the needle straight down through the center ring of the gray stopper (see illustrations). You should feel a slight resistance and then a "pop" as the needle goes through the center of the stopper. Look for the needle tip inside the open stopper window. If the needle is not correctly lined up with the center of the stopper, you will feel constant resistance as it goes through the stopper and no "pop". The needle may enter at an angle and bend, break or prevent you from adding diluent into the ENBREL[®] vial.



12. Push the plunger down **VERY SLOWLY** until all liquid from the syringe is in the ENBREL[®] vial. Adding the liquid too fast will cause foaming (bubbles).



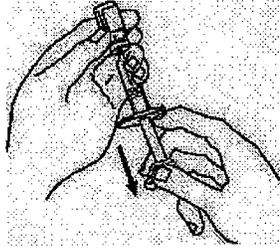
13. Leave the syringe in place. Gently swirl the ENBREL[®] vial in a circular motion to dissolve the powder.



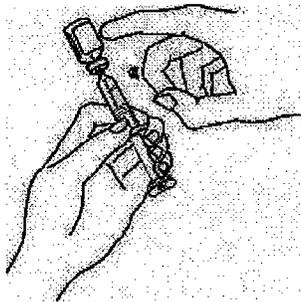
DO NOT SHAKE. Wait until all the powder dissolves (usually less than 10 minutes). The solution should be clear and colorless. After the powder has completely dissolved, foam (bubbles) may still be present. This is normal. **Do not inject the solution if it is discolored, contains lumps, flakes, or particles.** If all the powder in the ENBREL[®] vial is not dissolved or there are particles present after 10 minutes, call 1-888-4ENBREL (1-888-436-2735) for assistance.

14. With the needle in the ENBREL[®] vial, turn the vial upside down. Hold the syringe at eye level and slowly pull the plunger down to the unit markings on the side of the syringe that correspond with your child's dose. Make sure to keep the tip of the

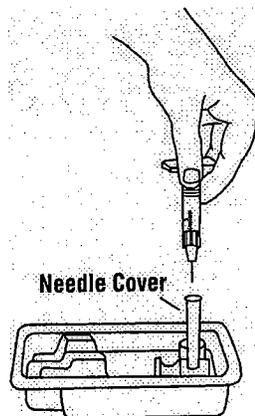
needle in the solution. Some white foam may remain in the ENBREL[®] vial. This is normal.



15. With the needle still inserted in the ENBREL[®] vial, check for air bubbles in the syringe. Gently tap the syringe to make any air bubbles rise to the top of the syringe. Slowly push the plunger up to remove the air bubbles. If you push solution back into the vial, slowly pull back on the plunger to draw the correct amount of solution back into the syringe.

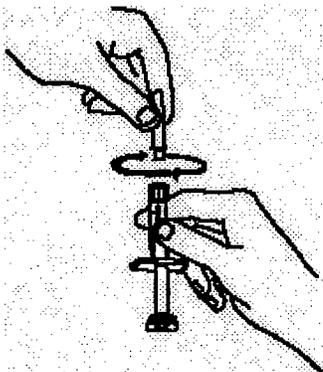


16. Remove the syringe and needle from the ENBREL[®] vial. Keep the needle attached to the syringe and insert the 25-gauge needle straight down into the needle cover in the ENBREL[®] dose tray.



You should hear a “snap” when the needle is secure in the needle cover. Once the needle is secure in the needle cover, untwist the 25-gauge needle from the syringe and dispose of the needle in your SHARPS container.

17. Twist the 27-gauge needle onto the syringe until it fits snugly. Do not remove the needle cover from the syringe. Place the syringe on your flat work surface until you are ready to inject ENBREL[®].



GO TO STEP 4: CHOOSING AND PREPARING AN INJECTION SITE.

STEP 3: Preparing Additional Doses from a Single ENBREL[®] Vial

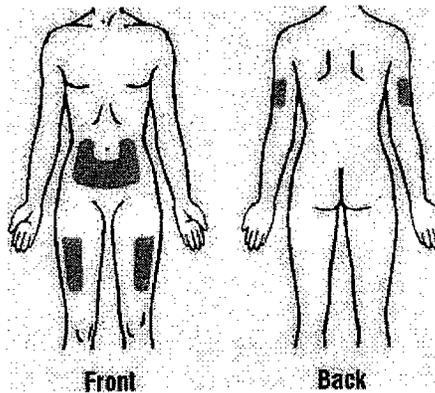
1. Select a clean, well-lit, flat work surface, such as a table.
2. The needles and syringes supplied with ENBREL[®] should not be reused. You will need new ones for each additional dose. Your healthcare provider will tell you what type of syringes (1 mL) and needles (25- and 27-gauge) to use. Alcohol swabs are available at the drug store. Place the sterile syringe with a 25-gauge needle (for withdrawing ENBREL[®]), a 27-gauge needle (for injecting ENBREL[®]) and two alcohol swabs on your flat work surface.
3. Take the vial of ENBREL[®] solution that is stored in the dose tray out of the refrigerator and place it on your flat work surface.
4. Check the mixing date you wrote on the sticker on the ENBREL[®] vial. **Discard the ENBREL[®] vial if more than 14 days have passed since the ENBREL[®] solution was mixed.**
5. Wash your hands with soap and warm water.

6. Use one alcohol swab to clean the gray stopper on the ENBREL[®] vial. Do not touch the stopper with your hands.
7. If the syringe and the 25-gauge needle are not pre-assembled, assemble them as instructed by your healthcare provider.
8. Open the wrapper that contains the 27-gauge needle by peeling apart the tabs and set the needle aside for later use. The 27-gauge needle will be used to inject the dose of ENBREL[®].
9. Hold the syringe and pull the needle cover straight off. Do not touch the needle or allow it to touch any surface. Place the needle cover (open side up) in the round space marked "N" in the ENBREL[®] dose tray.
10. Place the ENBREL[®] vial on your flat work surface. Hold the syringe with the needle facing up, and gently pull back the plunger to pull a small amount of air into the syringe. Then, insert the 25-gauge needle straight down through the center ring of the gray stopper. You should feel a slight resistance and then a "pop" as the needle goes through the center of the stopper. Look for the needle tip inside the open stopper window. If the needle is not correctly lined up with the center of the stopper, you will feel constant resistance as it goes through the stopper and no "pop". The needle may enter at an angle and bend, break, or prevent proper withdrawal of ENBREL[®] solution from the vial.
11. Keep the needle in the ENBREL[®] vial and turn the vial upside down. Hold the syringe at eye level, and slowly pull the plunger down to the unit markings on the syringe that correspond to your child's dose. As the amount of solution in the ENBREL[®] vial drops, you may need to pull the needle back just enough to keep the tip of the needle in the solution.
12. With the needle still inserted in the ENBREL[®] vial, check for air bubbles in the syringe. Gently tap the syringe to make any air bubbles rise to the top of the syringe. Slowly push the plunger up to remove the air bubbles. If you push solution back into the ENBREL[®] vial, slowly pull back on the plunger to again draw the correct amount of solution back into the syringe.
13. Remove the syringe and needle from the ENBREL[®] vial. Keep the needle attached to the syringe and insert the 25-gauge needle straight down into the needle cover in the ENBREL[®] dose tray. You should hear a "snap" when the needle is secure in the needle cover. Once the needle is secure in the needle cover, remove the 25-gauge needle from the syringe and dispose of the needle in a puncture-resistant container.

14. Twist the 27-gauge needle onto the tip of the syringe until it fits snugly. Do not remove the needle cover from the syringe. Place the syringe on your flat work surface until you are ready to inject ENBREL®.

STEP 4: Choosing and Preparing an Injection Site

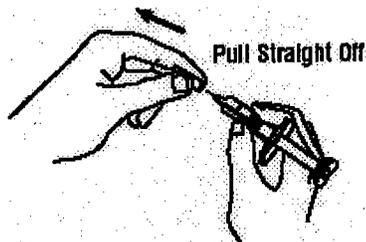
1. Three recommended injection sites for ENBREL® include: (1) the front of the middle thighs; (2) the abdomen, except for the two-inch area right around the navel; and, (3) the outer area of the upper arms.



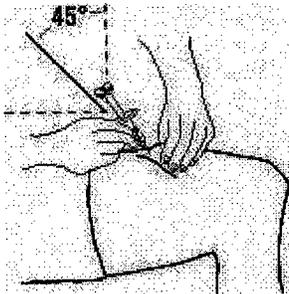
2. Rotate the site for each injection. Do not inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars or stretch marks.
3. If you have psoriasis, you should try not to inject directly into any raised, thick, red, or scaly skin patches (“psoriatic skin lesions”).
4. To prepare the area of skin where ENBREL® is to be injected, wipe the injection site with a new alcohol swab. **Do not touch this area again before giving the injection.**

STEP 5: Injecting the ENBREL® Solution

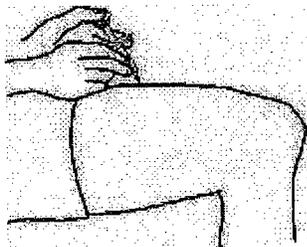
1. Pick up the syringe from your flat work surface. Hold the barrel of the syringe with one hand and pull the needle cover straight off. Do not touch the needle or allow it to touch any surface. Do not touch or bump the plunger. Doing so could cause the liquid to leak out.



2. With one hand, gently pinch the cleaned area of skin and hold it firmly. With the other hand, hold the syringe (like a pencil) at a 45-degree angle to the skin.



3. With a quick, "dart-like" motion, push the needle into the skin.
4. After the needle is inserted, let go of the skin. Pull the plunger back slightly. If no blood appears in the syringe, slowly push the plunger all the way down to inject ENBREL®.



If blood comes into the syringe, do not inject ENBREL® because the needle has entered a blood vessel. Withdraw the needle and repeat the steps to prepare for an injection. Do not use the same syringe and needle. Dispose of the used needle and syringe in a puncture-resistant container.

5. When the syringe is empty, pull the needle out of the skin, being careful to keep it at the same angle as inserted.
6. There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site for 10 seconds. Do not rub the injection site. If needed, you may cover the injection site with a bandage.
7. If your doctor has instructed you to take two ENBREL® injections on the same day, repeat the steps to prepare and give an injection of ENBREL®. Choose and prepare a new injection site for the second injection.
8. **FOR USE IN CHILDREN** - If there is enough solution left in the ENBREL® vial for another dose, refrigerate the ENBREL® vial (in the dose tray) after use. Otherwise,

discard the ENBREL[®] vial and any remaining solution.

STEP 6: Disposing of Supplies

- The syringe, needles, and vial adapter should **NEVER** be reused. **NEVER** recap a needle.
- Dispose of both the used needle and syringe in a puncture-resistant container. A SHARPS container made specifically for disposing of used syringes and needles may be used. **Do not** recycle the container.
- Keep the container out of the reach of children. When the container is about two-thirds full, dispose of it as instructed by your/your child's healthcare provider. Follow any special state or local laws regarding the proper disposal of needles and syringes.
- The ENBREL[®] vials, vial adapters, and used alcohol swabs should be placed in the trash. The dose tray and cover may be recycled.

A healthcare provider familiar with ENBREL[®] should answer all questions. A toll-free information service is also available: 1-888-4ENBREL (1-888-436-2735).

AMGEN[®]

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