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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<sub>H2</sub> domain, the C<sub>H3</sub> domain  
14 and hinge region, but not the C<sub>H1</sub> 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 $\alpha$  and TNF $\beta$  (lymphotoxin alpha [LT $\alpha$ ]) to cell surface TNFRs, rendering TNF biologically  
45 inactive. Cells expressing transmembrane TNF that bind ENBREL<sup>®</sup> 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<sup>®</sup> by a single subcutaneous (SC) injection to 25 patients  
53 with RA, a mean  $\pm$  standard deviation half-life of  $102 \pm 30$  hours was observed with a clearance of  
54  $160 \pm 80$  mL/hr. A maximum serum concentration (C<sub>max</sub>) of  $1.1 \pm 0.6$  mcg/mL and time to C<sub>max</sub>  
55 of  $69 \pm 34$  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<sub>max</sub> was  $2.4 \pm 1.0$  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<sub>0-72 hr</sub> (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<sup>®</sup> once weekly and those treated with 25 mg ENBREL<sup>®</sup> twice  
64 weekly. The mean ( $\pm$  standard deviation) C<sub>max</sub>, C<sub>min</sub>, and partial AUC were  $2.4 \pm 1.5$  mg/L,  $1.2 \pm$   
65  $0.7$  mg/L, and  $297 \pm 166$  mg $\cdot$ h/L, respectively, for patients treated with 50 mg ENBREL<sup>®</sup> once  
66 weekly (N = 21); and  $2.6 \pm 1.2$  mg/L,  $1.4 \pm 0.7$  mg/L, and  $316 \pm 135$  mg $\cdot$ h/L for patients treated  
67 with 25 mg ENBREL<sup>®</sup> 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<sup>®</sup> disposition.

71 Patients with JRA (ages 4 to 17 years) were administered 0.4 mg/kg of ENBREL<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> once weekly will result in C<sub>max</sub> 11% higher, and C<sub>min</sub>  
76 20% lower at steady state as compared to administration of 0.4 mg/kg of ENBREL<sup>®</sup> 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<sup>®</sup> in children < 4 years of age have not been studied.

80

## 81 **CLINICAL STUDIES**

### 82 **Adult Rheumatoid Arthritis**

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

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

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

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

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

117 or the combination of ENBREL<sup>®</sup> and MTX initiated concurrently (at the same doses as above).  
 118 The study evaluated ACR response, Sharp radiographic score and safety.

119 **Clinical Response**

120 A higher percentage of patients treated with ENBREL<sup>®</sup> and ENBREL<sup>®</sup> in combination with MTX  
 121 achieved ACR 20, ACR 50, and ACR 70 responses and Major Clinical Responses than in the  
 122 comparison groups. The results of Studies I, II, and III are summarized in Table 1. The results of  
 123 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 N = 80	ENBREL <sup>®a</sup> N = 78	MTX/ Placebo N = 30	MTX/ ENBREL <sup>®a</sup> N = 59	MTX N = 217	ENBREL <sup>®a</sup> N = 207
<b><u>ACR 20</u></b>						
Month 3	23%	62% <sup>b</sup>	33%	66% <sup>b</sup>	56%	62%
Month 6	11%	59% <sup>b</sup>	27%	71% <sup>b</sup>	58%	65%
Month 12	NA	NA	NA	NA	65%	72%
<b><u>ACR 50</u></b>						
Month 3	8%	41% <sup>b</sup>	0%	42% <sup>b</sup>	24%	29%
Month 6	5%	40% <sup>b</sup>	3%	39% <sup>b</sup>	32%	40%
Month 12	NA	NA	NA	NA	43%	49%
<b><u>ACR 70</u></b>						
Month 3	4%	15% <sup>b</sup>	0%	15% <sup>b</sup>	7%	13% <sup>c</sup>
Month 6	1%	15% <sup>b</sup>	0%	15% <sup>b</sup>	14%	21% <sup>c</sup>
Month 12	NA	NA	NA	NA	22%	25%

<sup>a</sup> 25 mg ENBREL<sup>®</sup> SC twice weekly.

<sup>b</sup> p < 0.01, ENBREL<sup>®</sup> vs. placebo.

<sup>c</sup> p < 0.05, ENBREL<sup>®</sup> vs. MTX.

**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)
<b>ACR N<sup>a, b</sup></b>			
Month 12	40	47	63 <sup>c</sup>
<b>ACR 20</b>			
Month 12	59%	66%	75% <sup>c</sup>
<b>ACR 50</b>			
Month 12	36%	43%	63% <sup>c</sup>
<b>ACR 70</b>			
Month 12	17%	22%	40% <sup>c</sup>
<b>Major Clinical Response<sup>d</sup></b>	6%	10%	24% <sup>c</sup>

<sup>a</sup> Values are medians.

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

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

<sup>d</sup> Major clinical response is achieving an ACR 70 response for a continuous 6-month period.

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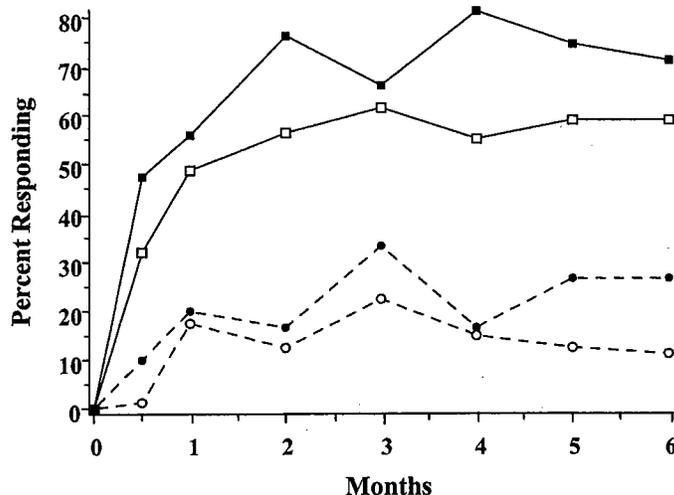
126 The time course for ACR 20 response rates for patients receiving placebo or 25 mg ENBREL® in  
 127 Studies I and II is summarized in Figure 1. The time course of responses to ENBREL® in Study III  
 128 was similar.

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

-○- Placebo, Study I (placebo alone)      -□- 25 mg ENBREL<sup>®</sup>, Study I (ENBREL<sup>®</sup> alone)  
 -●- Placebo, Study II (placebo + MTX)      -■- 25 mg ENBREL<sup>®</sup>, Study II (ENBREL<sup>®</sup> + MTX)



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

139 In Study III, ACR response rates and improvement in all the individual ACR response criteria were  
 140 maintained through 24 months of ENBREL<sup>®</sup> therapy. Over the 2-year study, 23% of ENBREL<sup>®</sup>  
 141 patients achieved a major clinical response, defined as maintenance of an ACR 70 response over a  
 142 6-month period.

143 The results of the components of the ACR response criteria for Study I are shown in Table 3.  
 144 Similar results were observed for ENBREL<sup>®</sup>-treated patients in Studies II and III.

**Table 3:  
Components of ACR Response in Study I**

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

<sup>\*</sup> Results at 6 months showed similar improvement.

<sup>a</sup> 25 mg ENBREL<sup>®</sup> SC twice weekly.

<sup>b</sup> Scale 0-71.

<sup>c</sup> Scale 0-68.

<sup>d</sup> Visual analog scale; 0 = best, 10 = worst.

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

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

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147 After discontinuation of ENBREL<sup>®</sup>, symptoms of arthritis generally returned within a month.  
148 Reintroduction of treatment with ENBREL<sup>®</sup> after discontinuations of up to 18 months resulted in  
149 the same magnitudes of response as patients who received ENBREL<sup>®</sup> without interruption of  
150 therapy based on results of open-label studies.

151 Continued durable responses were seen for over 60 months in open-label extension treatment trials  
152 when patients received ENBREL<sup>®</sup> without interruption. A substantial number of patients who  
153 initially received concomitant MTX or corticosteroids were able to reduce their doses or  
154 discontinue these concomitant therapies while maintaining their clinical responses.

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

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165 **Physical Function Response**

166 In Studies I, II, and III, physical function and disability were assessed using the Health Assessment  
 167 Questionnaire (HAQ).<sup>1</sup> Additionally, in Study III, patients were administered the SF-36<sup>2</sup> Health  
 168 Survey. In Studies I and II, patients treated with 25 mg ENBREL<sup>®</sup> twice weekly showed greater  
 169 improvement from baseline in the HAQ score beginning in month 1 through month 6 in comparison  
 170 to placebo (p < 0.001) for the HAQ disability domain (where 0 = none and 3 = severe). In Study I,  
 171 the mean improvement in the HAQ score from baseline to month 6 was 0.6 (from 1.6 to 1.0) for the  
 172 25 mg ENBREL<sup>®</sup> group and 0 (from 1.7 to 1.7) for the placebo group. In Study II, the mean  
 173 improvement from baseline to month 6 was 0.6 (from 1.5 to 0.9) for the ENBREL<sup>®</sup>/MTX group  
 174 and 0.2 (from 1.3 to 1.2) for the placebo/MTX group. In Study III, the mean improvement in the  
 175 HAQ score from baseline to month 6 was 0.7 (from 1.5 to 0.7) for 25 mg ENBREL<sup>®</sup> twice weekly.  
 176 All subdomains of the HAQ in Studies I and III were improved in patients treated with ENBREL<sup>®</sup>.

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

182 In Study IV, median HAQ scores improved from baseline levels of 1.8, 1.8, and 1.8 to 1.1, 1.0, and  
 183 0.6 at 12 months in the MTX, ENBREL<sup>®</sup>, and ENBREL<sup>®</sup>/MTX combination treatment groups,  
 184 respectively (combination versus both MTX and ENBREL<sup>®</sup>, p < 0.01). Twenty-nine percent of  
 185 patients in the MTX alone treatment group had an improvement of HAQ of at least one unit versus  
 186 40% and 51% in the ENBREL<sup>®</sup> alone and the ENBREL<sup>®</sup>/MTX combination treatment groups,  
 187 respectively.

188 **Radiographic Response**

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

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**Table 4:  
 Mean Radiographic Change Over 6 and 12 Months in Study III**

		MTX	25 mg ENBREL <sup>®</sup>	MTX/ENBREL <sup>®</sup> (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<sup>®</sup>

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

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

205 In Study IV, less radiographic progression (TSS) was observed with ENBREL<sup>®</sup> in combination  
 206 with MTX compared with ENBREL<sup>®</sup> alone or MTX alone at month 12 (Table 5). In the MTX  
 207 treatment group 55% of patients experienced no radiographic progression (TSS change  $\leq 0.0$ ) at 12  
 208 months compared to 63% and 76% in the ENBREL<sup>®</sup> alone and the ENBREL<sup>®</sup>/MTX combination  
 209 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 <sup>®</sup> (N = 212)*	ENBREL <sup>®</sup> /MTX (N = 218)*
Total Sharp Scores (TSS)	2.80 (1.08, 4.51)	0.52 <sup>a</sup> (-0.10, 1.15)	-0.54 <sup>b,c</sup> (-1.00, -0.07)
Erosion Score (ES)	1.68 (0.61, 2.74)	0.21 <sup>a</sup> (-0.20, 0.61)	-0.30 <sup>b</sup> (-0.65, 0.04)
Joint Space Narrowing Score (JSN)	1.12 (0.34, 1.90)	0.32 (0.00, 0.63)	-0.23 <sup>b,c</sup> (-0.45, -0.02)

\* Analyzed radiographic ITT population.

<sup>a</sup> p < 0.05 for comparison of ENBREL<sup>®</sup> vs MTX

<sup>b</sup> p < 0.05 for comparison of ENBREL<sup>®</sup>/MTX vs MTX

<sup>c</sup> p < 0.05 for comparison of ENBREL<sup>®</sup>/MTX vs ENBREL<sup>®</sup>

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213 **Once Weekly Dosing**

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

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

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

233 In part 1 of the study, 51 of 69 (74%) patients demonstrated a clinical response and entered part 2.  
234 In part 2, 6 of 25 (24%) patients remaining on ENBREL<sup>®</sup> experienced a disease flare compared to  
235 20 of 26 (77%) patients receiving placebo ( $p = 0.007$ ). From the start of part 2, the median time to  
236 flare was  $\geq 116$  days for patients who received ENBREL<sup>®</sup> and 28 days for patients who received  
237 placebo. Each component of the JRA core set criteria worsened in the arm that received placebo  
238 and remained stable or improved in the arm that continued on ENBREL<sup>®</sup>. The data suggested the  
239 possibility of a higher flare rate among those patients with a higher baseline ESR. Of patients who  
240 demonstrated a clinical response at 90 days and entered part 2 of the study, some of the patients  
241 remaining on ENBREL<sup>®</sup> continued to improve from month 3 through month 7, while those who  
242 received placebo did not improve.

243 The majority of JRA patients who developed a disease flare in part 2 and reintroduced ENBREL<sup>®</sup>  
244 treatment up to 4 months after discontinuation re-responded to ENBREL<sup>®</sup> therapy in open-label  
245 studies. Most of the responding patients who continued ENBREL<sup>®</sup> therapy without interruption  
246 have maintained responses for up to 48 months.

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

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251 **Psoriatic Arthritis**

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

265 Compared to placebo, treatment with ENBREL<sup>®</sup> resulted in significant improvements in measures  
 266 of disease activity (Table 6).

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**Table 6:  
 Components of Disease Activity in Psoriatic Arthritis**

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

<sup>a</sup> p < 0.001 for all comparisons between ENBREL<sup>®</sup> and placebo at 6 months.

<sup>b</sup> Scale 0-78.

<sup>c</sup> Scale 0-76.

<sup>d</sup> Likert scale; 0 = best, 5 = worst.

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

<sup>f</sup> Normal range: 0-0.79 mg/dL

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

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

#### 284 ***Radiographic Response***

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

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

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306 **Physical Function Response**

307 In the psoriatic arthritis study, physical function and disability were assessed using the HAQ  
308 Disability Index (HAQ-DI)<sup>1</sup> and the SF-36<sup>2</sup> Health Survey. Patients treated with 25 mg ENBREL<sup>®</sup>  
309 twice weekly showed greater improvement from baseline in the HAQ-DI score (mean decreases of  
310 54% at both months 3 and 6) in comparison to placebo (mean decreases of 6% at both months 3 and  
311 6) (p <0.001). At months 3 and 6, patients treated with ENBREL<sup>®</sup> showed greater improvement  
312 from baseline in the SF-36 physical component summary score compared to patients treated with  
313 placebo, and no worsening in the SF-36 mental component summary score. Improvements in  
314 physical function and disability measures were maintained for up to 2 years through the open-label  
315 portion of the study.

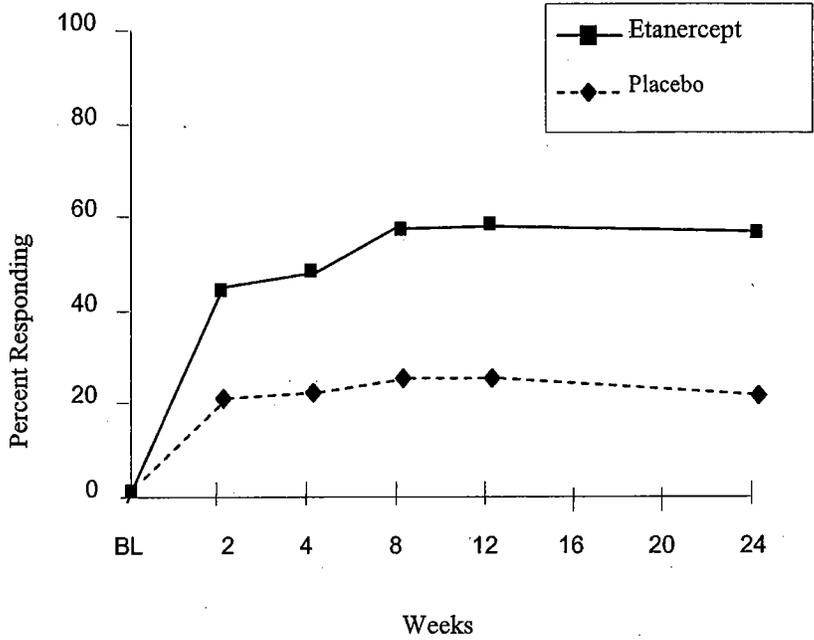
316 **Ankylosing Spondylitis**

317 The safety and efficacy of ENBREL<sup>®</sup> were assessed in a randomized, double-blind,  
318 placebo-controlled study in 277 patients with active ankylosing spondylitis. Patients were between  
319 18 and 70 years of age and had ankylosing spondylitis as defined by the modified New York  
320 Criteria for Ankylosing Spondylitis.<sup>5</sup> Patients were to have evidence of active disease based on  
321 values of  $\geq 30$  on a 0-100 unit Visual Analog Scale (VAS) for the average of morning stiffness  
322 duration and intensity, and 2 of the following 3 other parameters: a) patient global assessment, b)  
323 average of nocturnal and total back pain, and c) the average score on the Bath Ankylosing  
324 Spondylitis Functional Index (BASFI). Patients with complete ankylosis of the spine were  
325 excluded from study participation. Patients taking hydroxychloroquine, sulfasalazine, methotrexate  
326 or prednisone ( $\leq 10$  mg/day) could continue these drugs at stable doses for the duration of the study.  
327 Doses of 25 mg ENBREL<sup>®</sup> or placebo were administered SC twice a week for 6 months.

328 The primary measure of efficacy was a 20% improvement in the Assessment in Ankylosing  
329 Spondylitis (ASAS) response criteria.<sup>6</sup> Compared to placebo, treatment with ENBREL<sup>®</sup> resulted in  
330 improvements in the ASAS and other measures of disease activity (Figure 2 and Table 7).

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**Figure 2: ASAS 20 Responses in Ankylosing Spondylitis**



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

**Table 7:**  
**Components of Ankylosing Spondylitis Disease Activity**

Mean values at time points	Placebo N = 139		ENBREL <sup>®a</sup> N = 138	
	Baseline	6 Months	Baseline	6 Months
ASAS response criteria				
Patient global assessment <sup>b</sup>	63	56	63	36
Back pain <sup>c</sup>	62	56	60	34
BASFI <sup>d</sup>	56	55	52	36
Inflammation <sup>e</sup>	64	57	61	33
Acute phase reactants				
CRP (mg/dL) <sup>f</sup>	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

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

<sup>b</sup> Measured on a Visual Analog Scale (VAS) scale with 0 = "none" and 100 = "severe."

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

<sup>d</sup> Bath Ankylosing Spondylitis Functional Index (BASFI), average of 10 questions.

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

<sup>f</sup> C-reactive protein (CRP) normal range: 0-1.0 mg/dL.

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### 363 **Plaque Psoriasis**

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

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

376 Study II evaluated 611 patients who received placebo or ENBREL<sup>®</sup> SC at doses of 25 mg or 50 mg  
377 twice a week for 3 months. After 3 months of randomized blinded treatment, patients in all three  
378 arms began receiving open-label ENBREL<sup>®</sup> at 25 mg twice weekly for 9 additional months.

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

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

391 Patients in all treatment groups and in both studies had a median baseline PASI score ranging from  
392 15 to 17; and the percentage of patients with baseline sPGA classifications ranged from 54% to  
393 66% for moderate, 17% to 26% for marked, and 1% to 5% for severe. Across all treatment groups,  
394 the percentage of patients who previously received systemic therapy for psoriasis ranged from 61%  
395 to 65% in Study I, and 71% to 75% in Study II; and those who previously received phototherapy  
396 ranged from 44% to 50% in Study I, and 72% to 73% in Study II.

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

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**Table 8: Study I Outcomes at 3 and 6 Months**

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

<sup>a</sup> p = 0.001 compared with placebo

<sup>b</sup> p < 0.0001 compared with placebo

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**Table 9: Study II Outcomes at 3 Months**

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

<sup>a</sup> p < 0.0001 compared with placebo

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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.

415 In Study I, in patients who were PASI 75 responders at 3 months, retreatment with open-label  
416 ENBREL<sup>®</sup> after discontinuation of up to 5 months resulted in a similar proportion of responders as  
417 was seen during the initial double-blind portion of the study.

418 In Study II, most patients initially randomized to 50 mg twice a week continued in the study after  
419 month 3 and had their ENBREL<sup>®</sup> dose decreased to 25 mg twice a week. Of the 91 patients who  
420 were PASI 75 responders at month 3, 70 (77%) maintained their PASI 75 response at month 6.

421 Efficacy and safety of ENBREL<sup>®</sup> treatment beyond 12 months has not been adequately evaluated in  
422 patients with psoriasis.

## 423 **INDICATIONS AND USAGE**

424 ENBREL<sup>®</sup> is indicated for reducing signs and symptoms, inducing major clinical response,  
425 inhibiting the progression of structural damage, and improving physical function in patients with  
426 moderately to severely active rheumatoid arthritis. ENBREL<sup>®</sup> can be initiated in combination with  
427 methotrexate (MTX) or used alone.

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

431 ENBREL<sup>®</sup> is indicated for reducing signs and symptoms, inhibiting the progression of structural  
432 damage of active arthritis, and improving physical function in patients with psoriatic arthritis.  
433 ENBREL<sup>®</sup> can be used in combination with methotrexate in patients who do not respond  
434 adequately to methotrexate alone.

435 ENBREL<sup>®</sup> is indicated for reducing signs and symptoms in patients with active ankylosing  
436 spondylitis.

437 ENBREL<sup>®</sup> is indicated for the treatment of adult patients (18 years or older) with chronic moderate  
438 to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

## 439 **CONTRAINDICATIONS**

440 ENBREL<sup>®</sup> should not be administered to patients with sepsis or with known hypersensitivity to  
441 ENBREL<sup>®</sup> or any of its components.

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447 **WARNINGS**

448 **INFECTIONS**

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

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

473 **Neurologic Events**

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

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486 **Hematologic Events**

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

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

498 **Malignancies**

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

510 **PRECAUTIONS**

511 **General**

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

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

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521 **Information for Patients**

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

533 **Patients with Heart Failure**

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

545 **Immunosuppression**

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

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559 **Immunizations**

560 Most psoriatic arthritis patients receiving ENBREL<sup>®</sup> were able to mount effective B-cell immune  
561 responses to pneumococcal polysaccharide vaccine, but titers in aggregate were moderately lower  
562 and fewer patients had two-fold rises in titers compared to patients not receiving ENBREL<sup>®</sup>. The  
563 clinical significance of this is unknown. Patients receiving ENBREL<sup>®</sup> may receive concurrent  
564 vaccinations, except for live vaccines. No data are available on the secondary transmission of  
565 infection by live vaccines in patients receiving ENBREL<sup>®</sup> (see **PRECAUTIONS:**  
566 **Immunosuppression**).

567 It is recommended that JRA patients, if possible, be brought up to date with all immunizations in  
568 agreement with current immunization guidelines prior to initiating ENBREL<sup>®</sup> therapy. Patients  
569 with a significant exposure to varicella virus should temporarily discontinue ENBREL<sup>®</sup> therapy and  
570 be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

571 **Autoimmunity**

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

578 **Drug Interactions**

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

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

586 Patients in a clinical study who were on established therapy with sulfasalazine, to which ENBREL<sup>®</sup>  
587 was added, were noted to develop a mild decrease in mean neutrophil counts in comparison to  
588 groups treated with either ENBREL<sup>®</sup> or sulfasalazine alone. The clinical significance of this  
589 observation is unknown.

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592

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

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

597 **Pregnancy (Category B)**

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

603 ***Pregnancy Registry:*** To monitor outcomes of pregnant women exposed to ENBREL<sup>®</sup>, a pregnancy  
604 registry has been established. Physicians are encouraged to register patients by calling 1-877-311-  
605 8972.

606 **Nursing Mothers**

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

611 **Geriatric Use**

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

616 **Pediatric Use**

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

622 The safety and efficacy of ENBREL<sup>®</sup> in pediatric patients with plaque psoriasis have not been  
623 studied.

624

625

626

627 **ADVERSE REACTIONS**

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

630 ENBREL<sup>®</sup> has been studied in 1442 patients with RA, followed for up to 80 months, in 169  
631 patients with psoriatic arthritis for up to 24 months, in 222 patients with ankylosing spondylitis for  
632 up to 10 months, and 1261 patients with plaque psoriasis for up to 15 months. In controlled trials,  
633 the proportion of ENBREL<sup>®</sup>-treated patients who discontinued treatment due to adverse events was  
634 approximately 4% in the indications studied. The vast majority of these patients were treated with  
635 25 mg SC twice weekly. In plaque psoriasis studies, ENBREL<sup>®</sup> doses studied were 25 mg SC once  
636 a week, 25 mg SC twice a week, and 50 mg SC twice a week.

637

638 **Injection Site Reactions**

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

649 **Infections**

650 In controlled trials, there were no differences in rates of infection among RA, psoriatic arthritis,  
651 ankylosing spondylitis, and plaque psoriasis patients treated with ENBREL<sup>®</sup> and those treated with  
652 placebo (or MTX for RA and psoriatic arthritis patients). The most common type of infection was  
653 upper respiratory infection, which occurred at a rate of approximately 20% among both ENBREL<sup>®</sup>-  
654 and placebo-treated patients in RA, psoriatic arthritis, and AS trials, and at a rate of approximately  
655 12% among both ENBREL<sup>®</sup>- and placebo-treated patients in plaque psoriasis trials in the first 3  
656 months of treatment.

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

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

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

678 In clinical trials in plaque psoriasis, serious infections experienced by ENBREL<sup>®</sup>-treated patients  
679 have included: cellulitis, gastroenteritis, pneumonia, abscess, and osteomyelitis.

## 680 **Malignancies**

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

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

## 701 **Immunogenicity**

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

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

716

## 717 **Autoantibodies**

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

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

732 **Other Adverse Reactions**

733 Table 10 summarizes events reported in at least 3% of all patients with higher incidence in patients  
734 treated with ENBREL<sup>®</sup> compared to controls in placebo-controlled RA-trials (including the  
735 combination methotrexate trial) and relevant events from Study III. In placebo-controlled plaque  
736 psoriasis trials, the percentages of patients reporting injection site reactions were lower in the  
737 placebo dose group (6.4%) than in the ENBREL<sup>®</sup> dose groups (15.5%) in Studies I and II.  
738 Otherwise, the percentages of patients reporting adverse events in the 50 mg twice a week dose  
739 group were similar to those observed in the 25 mg twice a week dose group or placebo group. In  
740 psoriasis Study I, there were no serious adverse events of worsening psoriasis following withdrawal  
741 of study drug. However, adverse events of worsening psoriasis including three serious adverse  
742 events were observed during the course of the clinical trials. Urticaria and non-infectious hepatitis  
743 were observed in a small number of patients and angioedema was observed in one patient in clinical  
744 studies. Urticaria and angioedema have also been reported in spontaneous post-marketing reports.  
745 Adverse events in psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis trials were similar  
746 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 <sup>†</sup> (N = 152)	ENBREL <sup>®</sup> (N = 349)	MTX (N = 217)	ENBREL <sup>®</sup> (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<sup>®</sup>-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<sup>®</sup> N = 213).

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

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

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

### 773 **Adverse Reactions in Patients with JRA**

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

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

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

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

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

#### 797 **Patients with Heart Failure**

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

#### 806 **Adverse Reaction Information from Spontaneous Reports**

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

810 Additional adverse events are listed by body system below:

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

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

829 **OVERDOSAGE**

830 The maximum tolerated dose of ENBREL<sup>®</sup> has not been established in humans. Toxicology  
831 studies have been performed in monkeys at doses up to 30 times the human dose with no evidence  
832 of dose-limiting toxicities. No dose-limiting toxicities have been observed during clinical trials of  
833 ENBREL<sup>®</sup>. Single IV doses up to 60 mg/m<sup>2</sup> have been administered to healthy volunteers in an  
834 endotoxemia study without evidence of dose-limiting toxicities.

835 **DOSAGE AND ADMINISTRATION**

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

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

844 **Adult Plaque Psoriasis Patients**

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

849 Starting doses of ENBREL<sup>®</sup> of 25 mg or 50 mg per week were also shown to be efficacious. The  
850 proportion of responders were related to ENBREL<sup>®</sup> dosage (see **CLINICAL STUDIES**).

851 **JRA Patients**

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

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

### 863 **Preparation of ENBREL<sup>®</sup>**

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

868 The ENBREL<sup>®</sup> (etanercept) "Patient Information" insert contains more detailed instructions on the  
869 preparation of ENBREL<sup>®</sup>.

### 870 **Preparation of ENBREL<sup>®</sup> Using the Single-use Prefilled Syringe:**

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

### 874 **Preparation of ENBREL<sup>®</sup> Using the Multiple-use Vial:**

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

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

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

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

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

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

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

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

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

### 906 **Administration of ENBREL<sup>®</sup>**

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

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

### 913 **Storage and Stability**

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

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

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

### 925 **HOW SUPPLIED**

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

929 syringe of ENBREL<sup>®</sup> provides a dose equivalent to two 25 mg vials of lyophilized ENBREL<sup>®</sup>,  
930 when vials are reconstituted and administered as recommended.

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

936 **Rx Only**

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**AMGEN**<sup>®</sup>

**Wyeth**<sup>®</sup>

971  
972

973 **Manufactured by:**  
974 Immunex Corporation  
975 Thousand Oaks, CA 91320-1799  
976 U.S. License Number 1132  
977 Marketed by Amgen and Wyeth Pharmaceuticals  
978

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980

981 3XXXXXX- v23.1.1

982 Issue Date: xx/xx/xxxx

983 Immunex U.S. Patent Numbers:

984 5,395,760; 5,605,690; 5,945,397; 6,201,105; 6,572,852; Re. 36,755  
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1  
2  
3 **ENBREL®**  
4 **(etanercept)**  
5 *Multiple-use Vial*  
6 **PATIENT INFORMATION**  
7

8 **ENBREL®** (pronounced en-brel)

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

14 **What is ENBREL®?**

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

24 **How does ENBREL® work?**

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

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

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

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

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

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

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

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**Pregnancy Registry Update: 6/1/05**

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

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

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

### 93 Who should not take ENBREL®?

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

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

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

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

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

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Pregnancy Registry Update; 6/1/05

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106 Yes, you can take other medicines if your doctor has prescribed them or has told you it is  
107 OK to take them while you are taking ENBREL<sup>®</sup>. It is important that you tell your doctor  
108 about any other medicines (for example, high blood pressure medicine) you are taking for  
109 other conditions before you start taking ENBREL<sup>®</sup>. Taking ENBREL<sup>®</sup> with Kineret<sup>®</sup>  
110 (anakinra) is not recommended because this may increase your risk of getting a serious  
111 infection.

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

#### 114 **How do I take ENBREL<sup>®</sup>?**

115 ENBREL<sup>®</sup> is given by injection under the skin.

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

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

125 If you have psoriasis, the recommended starting dose of ENBREL<sup>®</sup> for adult patients is a  
126 50 mg dose twice a week (3 or 4 days apart) given for three months. After 3 months, your  
127 doctor will tell you to reduce your dose to 50 mg once per week. The 50 mg dose should  
128 be given as two 25 mg injections at two different sites.

129 Make sure you have been shown how to inject ENBREL<sup>®</sup> before you do it yourself. You  
130 can call your doctor or the ENBREL<sup>®</sup> toll-free information line at 1-888-4ENBREL  
131 (1-888-436-2735) if you have any questions about ENBREL<sup>®</sup> or about giving yourself or  
132 your child an injection. Someone you know can also help you with your injection.  
133 Remember to take this medicine just as your doctor has told you and do not miss any  
134 doses.

#### 135 **What should I do if I miss a dose of ENBREL<sup>®</sup>?**

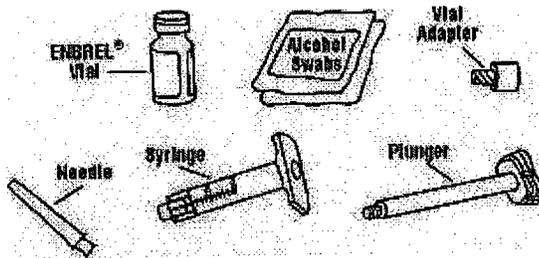
136 If you forget to take ENBREL<sup>®</sup> when you are supposed to, contact your doctor to find out  
137 when to take your next dose of ENBREL<sup>®</sup>.

#### 138 **What do I need to do to prepare and give an injection of ENBREL<sup>®</sup>?**

##### 139 **STEP 1: Setting up for an Injection**

- 140 1. Select a clean, well-lit, flat work surface, such as a table.
- 141 2. Take the ENBREL<sup>®</sup> dose tray out of the refrigerator and place it on your flat work  
142 surface.
- 143 3. Check the expiration date on the dose tray. If the expiration date has passed, do not  
144 use the dose tray. Also check to make sure the dose tray has seven items as pictured  
145 below:
- 146
- 147 • One prefilled diluent syringe containing 1 mL of diluent (liquid) with attached
  - 148 gray tip cap
  - 149 • One plunger
  - 150 • One ENBREL<sup>®</sup> vial
  - 151 • One 27-gauge ½ inch needle in hard plastic cover
  - 152 • One vial adapter
  - 153 • Two alcohol swabs
  - 154

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- 155
- 156 If the expiration date has passed, the seven items are not included in the dose tray or if  
157 any item looks damaged, contact your pharmacist or call 1-888-4ENBREL (1-888-436-  
158 2735) for assistance.

- 159 4. Wash your hands with soap and warm water.
- 160 5. Peel the paper seal off the dose tray and remove all items.
- 161
- 162 6. Inspect the volume of diluent in the syringe with the gray tip cap pointing down. Use  
163 the unit markings on the side of the syringe to make sure there is at least 1 mL of  
164 liquid in the syringe. If the level of liquid is below the 1 mL mark, do not use. Call  
165 1-888-4ENBREL (1-888-436-2735) for assistance.
- 166

## 167 **STEP 2: Preparing the ENBREL<sup>®</sup> Solution**

168 There are two methods for preparing the ENBREL<sup>®</sup> solution. For some children, one vial  
169 of ENBREL<sup>®</sup> solution can be used for more than one dose. The free-hand method should

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170 be used for children on ENBREL<sup>®</sup> who are using one vial of ENBREL<sup>®</sup> solution for  
 171 more than one dose. **You should not use the vial adapter method if you will be using**  
 172 **the vial more than once.** Ask your healthcare provider if you have questions about  
 173 which method to use.

174 • **The Vial Adapter Method**

175 Adult patients and larger children on ENBREL<sup>®</sup> may use the vial adapter device to assist  
 176 with mixing the powder with the liquid and withdrawing ENBREL<sup>®</sup>, and then use a  
 177 27-gauge needle to inject the dose. **This method should not be used for children using**  
 178 **multiple doses from the same vial of ENBREL<sup>®</sup>.** The instructions for using the vial  
 179 adapter method are in STEP 2A.

180 • **The Free-Hand Method**

181 In the free-hand method, a 25-gauge needle is used to assist with mixing the powder with  
 182 the liquid and withdrawing ENBREL<sup>®</sup>, and a 27-gauge needle is used to inject the dose.  
 183 Instructions for using the free-hand method are in STEP 2B.

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

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

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

194 The ENBREL<sup>®</sup> solution must be used within 14 days of the mixing date. You should  
 195 discard the ENBREL<sup>®</sup> vial and any remaining solution if it is not used within 14 days.  
 196 Do not mix any remaining liquid in one vial of ENBREL<sup>®</sup> solution with another.

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

201 **STEP 2A: Vial Adapter Method**

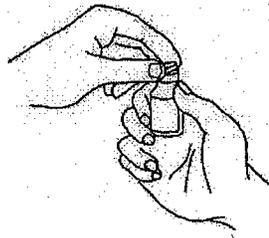
202 1. Remove the pink plastic cap from the ENBREL<sup>®</sup> vial. Do not remove the gray  
 203 stopper or silver metal ring around the top of the ENBREL<sup>®</sup> vial.

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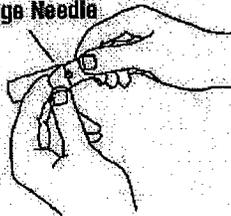
205

- 206 2. Place the ENBREL<sup>®</sup> vial on your flat work surface or turn your dose tray upside down  
 207 and place your ENBREL<sup>®</sup> vial in the round space marked "V". Use one alcohol swab  
 208 to clean the gray stopper on the ENBREL<sup>®</sup> vial. Do not touch the gray stopper with  
 209 your hands.

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- 210 3. Open the wrapper that contains the 27-gauge needle by peeling apart the tabs and set  
 211 the needle aside for later use.

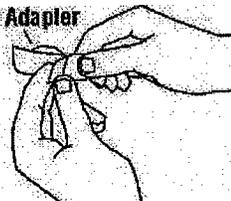
27-Gauge Needle



212  
 213

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

Vial Adapter

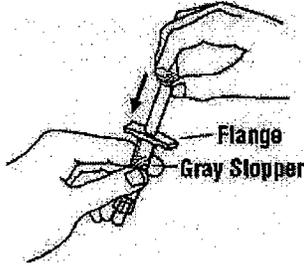


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 217

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

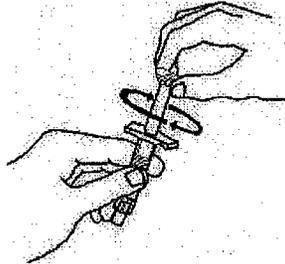
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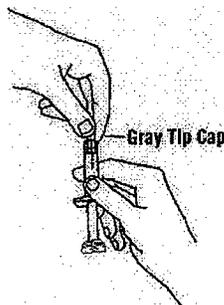
- 220 6. Attach the plunger to the gray rubber stopper in the syringe by turning the plunger  
221 clockwise until a slight resistance is felt.



222

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

227



228

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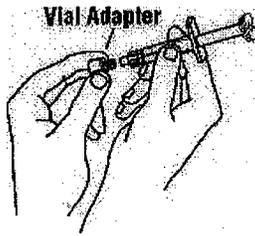
- 230 8. Once the gray tip cap is removed, pick up the vial adapter with your free hand. Twist  
231 the vial adapter onto the syringe until a slight resistance is felt. Do not over-tighten.

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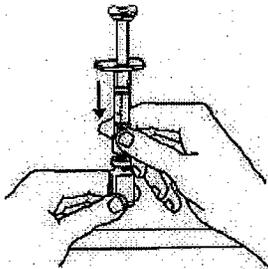
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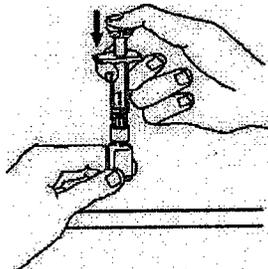
- 234 9. Hold the ENBREL<sup>®</sup> vial upright on your flat work surface. Grasp the sides of the vial  
 235 adapter and place it over the top of the ENBREL<sup>®</sup> vial. Do not bump or touch the  
 236 plunger. Doing so could cause the liquid to leak out. Insert the vial adapter into the  
 237 gray stopper on the ENBREL<sup>®</sup> vial. The plastic spike inside the vial adapter should  
 238 puncture the gray stopper. The vial adapter should fit snugly.  
 239

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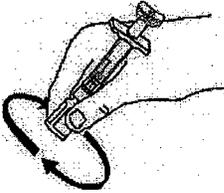
240

- 241 10. Hold the ENBREL<sup>®</sup> vial upright on your flat work surface and push the plunger down  
 242 until all the liquid from the syringe is in the ENBREL<sup>®</sup> vial. You may see foaming  
 243 (bubbles) in the vial. This is normal.  
 244



245

- 246 11. Gently swirl the ENBREL<sup>®</sup> vial in a circular motion to dissolve the powder. If you  
 247 used the dose tray to hold your ENBREL<sup>®</sup> vial, take the vial (with the vial adapter and  
 248 syringe still attached) out of the dose tray, and gently swirl the vial in a circular  
 249 motion to dissolve the powder.

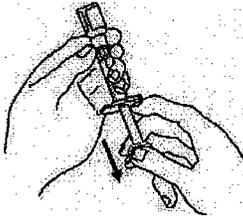


250

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

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

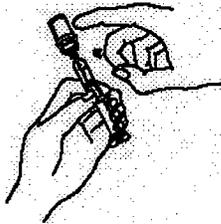
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262

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

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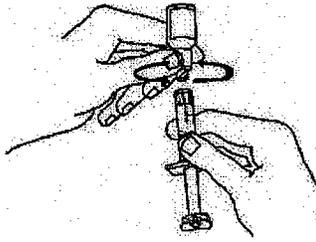


267

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

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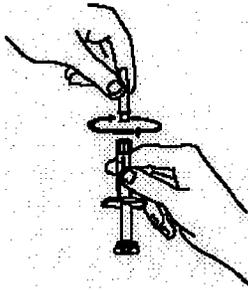
270 bump the plunger. Place the ENBREL<sup>®</sup> vial with the vial adapter on your flat work  
271 surface.



272

273 15. Continue to hold the barrel of the syringe. With your free hand, twist the 27-gauge  
274 needle onto the tip of the syringe until it fits snugly. Do not remove the needle cover  
275 from the syringe. Place the syringe on your flat work surface until you are ready to  
276 inject ENBREL<sup>®</sup>.  
277

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278

279

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

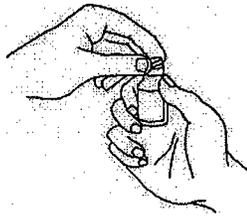
281 **STEP 2B: Free-Hand Method**

282 If you are preparing a dose from an ENBREL<sup>®</sup> vial that was previously used, go to  
283 STEP 3: Preparing Additional Doses from a Single ENBREL<sup>®</sup> Vial.

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

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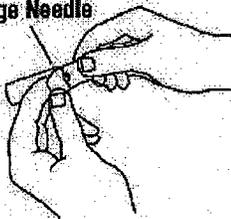
289

290 2. Place the ENBREL<sup>®</sup> vial on your flat work surface. Use one alcohol swab to clean  
291 the gray stopper on the ENBREL<sup>®</sup> vial. Do not touch the gray stopper with your  
292 hands.

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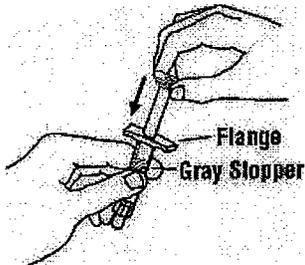
293 3. Open the wrapper that contains the 25-gauge needle by peeling apart the tabs and set  
294 the needle aside for later use. The 25-gauge needle will be used to mix the liquid with  
295 the powder and for withdrawing ENBREL<sup>®</sup> from the vial.

25-Gauge Needle



296

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



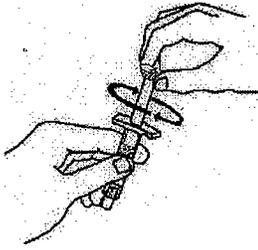
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298

299 5. Attach the plunger to the gray rubber stopper in the syringe by turning the plunger  
300 clockwise until a slight resistance is felt.  
301

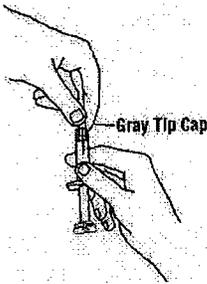
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302



303

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

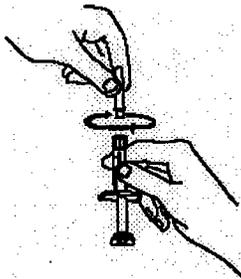


308

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

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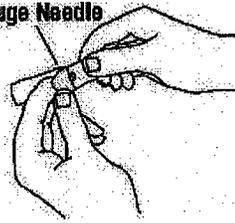
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- 314 8. Open the wrapper that contains the 27-gauge needle by peeling apart the tabs and set
- 315 the needle aside for later use. The 27-gauge needle will be used to inject the dose.

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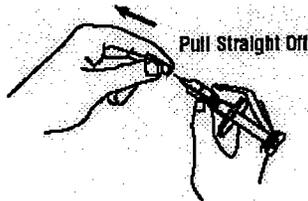
316

27-Gauge Needle



317

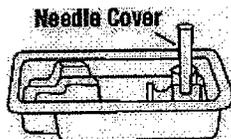
- 318 9. Pick up the syringe from your flat work surface. Hold the barrel of the syringe with  
 319 one hand, and pull the needle cover straight off. Do not touch the needle or allow it to  
 320 touch any surface. Do not touch or bump the plunger. Doing so could cause the  
 321 liquid to leak out.



322

- 323 10. Place the needle cover (open side up) in the round space marked "N" in the  
 324 ENBREL<sup>®</sup> dose tray.

325



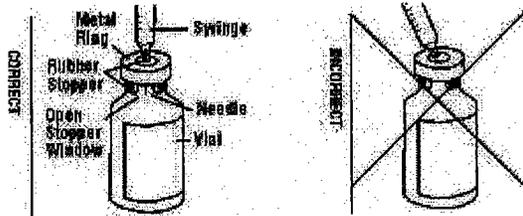
326

327

- 328 11. Place the ENBREL<sup>®</sup> vial on your flat work surface. Hold the syringe with the needle  
 329 facing up, and gently pull back on the plunger to pull a small amount of air into the  
 330 syringe. Then, insert the needle straight down through the center ring of the gray  
 331 stopper (see illustrations). You should feel a slight resistance and then a "pop" as the  
 332 needle goes through the center of the stopper. Look for the needle tip inside the open  
 333 stopper window. If the needle is not correctly lined up with the center of the stopper,  
 334 you will feel constant resistance as it goes through the stopper and no "pop". The  
 335 needle may enter at an angle and bend, break or prevent you from adding diluent into  
 336 the ENBREL<sup>®</sup> vial.  
 337

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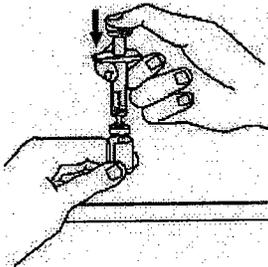


338  
339

340 12. Push the plunger down VERY SLOWLY until all liquid from the syringe is in the  
341 ENBREL<sup>®</sup> vial. Adding the liquid too fast will cause foaming (bubbles).

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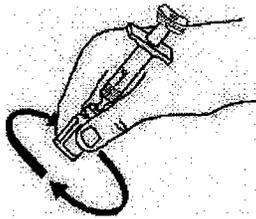
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343

344 13. Leave the syringe in place. Gently swirl the ENBREL<sup>®</sup> vial in a circular motion to  
345 dissolve the powder.

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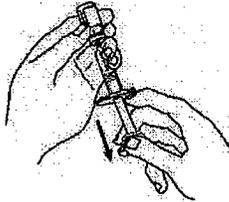
346

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

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

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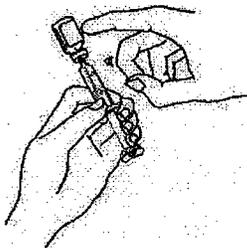
356 needle in the solution. Some white foam may remain in the ENBREL® vial. This is  
357 normal.



358

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

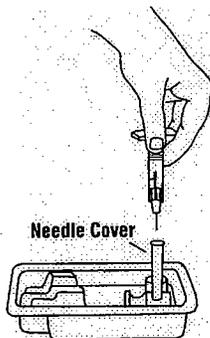
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364

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

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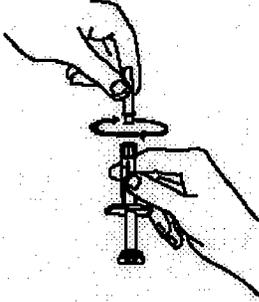
368

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

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

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376

377

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

### 379 **STEP 3: Preparing Additional Doses from a Single ENBREL® Vial**

380 1. Select a clean, well-lit, flat work surface, such as a table.

381 2. The needles and syringes supplied with ENBREL® should not be reused. You will  
 382 need new ones for each additional dose. Your healthcare provider will tell you what  
 383 type of syringes (1 mL) and needles (25- and 27-gauge) to use. Alcohol swabs are  
 384 available at the drug store. Place the sterile syringe with a 25-gauge needle (for  
 385 withdrawing ENBREL®), a 27-gauge needle (for injecting ENBREL®) and two  
 386 alcohol swabs on your flat work surface.

387 3. Take the vial of ENBREL® solution that is stored in the dose tray out of the  
 388 refrigerator and place it on your flat work surface.

389 4. Check the mixing date you wrote on the sticker on the ENBREL® vial. **Discard the**  
 390 **ENBREL® vial if more than 14 days have passed since the ENBREL® solution**  
 391 **was mixed.**

392 5. Wash your hands with soap and warm water.

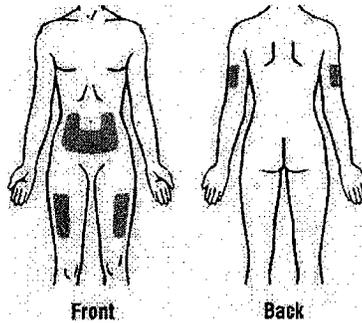
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- 393 6. Use one alcohol swab to clean the gray stopper on the ENBREL<sup>®</sup> vial. Do not touch  
394 the stopper with your hands.
- 395 7. If the syringe and the 25-gauge needle are not pre-assembled, assemble them as  
396 instructed by your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

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

430 **STEP 4: Choosing and Preparing an Injection Site**

- 431 1. Three recommended injection sites for ENBREL® include: (1) the front of the  
 432 middle thighs; (2) the abdomen, except for the two-inch area right around the  
 433 navel; and, (3) the outer area of the upper arms.  
 434  
 435



436

- 437 2. Rotate the site for each injection. Do not inject into areas where the skin is tender,  
 438 bruised, red, or hard. Avoid areas with scars or stretch marks.  
 439  
 440 3. If you have psoriasis, you should try not to inject directly into any raised, thick, red, or  
 441 scaly skin patches ("psoriatic skin lesions").  
 442  
 443 4. To prepare the area of skin where ENBREL® is to be injected, wipe the injection site  
 444 with a new alcohol swab. **Do not touch this area again before giving the injection.**

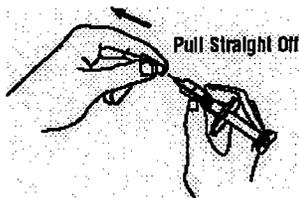
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446 **STEP 5: Injecting the ENBREL® Solution**

- 447 1. Pick up the syringe from your flat work surface. Hold the barrel of the syringe with  
 448 one hand and pull the needle cover straight off. Do not touch the needle or allow it to  
 449 touch any surface. Do not touch or bump the plunger. Doing so could cause the  
 450 liquid to leak out.  
 451

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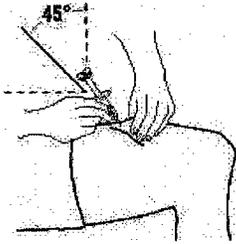
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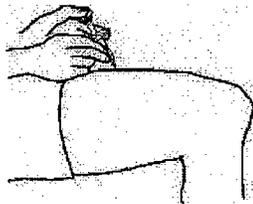
**Pregnancy Registry Update: 6/1/05**

- 454 | 2. With one hand, gently pinch the cleaned area of skin and hold it firmly. With the  
 455 | other hand, hold the syringe (like a pencil) at a 45-degree angle to the skin.  
 456 |



457  
 458

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



463  
 464

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.

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

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479 discard the ENBREL<sup>®</sup> vial and any remaining solution.  
480

481 **STEP 6: Disposing of Supplies**

482 • The syringe, needles, and vial adapter should **NEVER** be reused. **NEVER** recap a  
483 needle.

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484 • Dispose of both the used needle and syringe in a puncture-resistant container. A  
485 SHARPS container made specifically for disposing of used syringes and needles may  
486 be used. **Do not** recycle the container.

487 • Keep the container out of the reach of children. When the container is about  
488 two-thirds full, dispose of it as instructed by your/your child's healthcare provider.  
489 Follow any special state or local laws regarding the proper disposal of needles and  
490 syringes.

491 • The ENBREL<sup>®</sup> vials, vial adapters, and used alcohol swabs should be placed in the  
492 trash. The dose tray and cover may be recycled.

493 A healthcare provider familiar with ENBREL<sup>®</sup> should answer all questions. A toll-free  
494 information service is also available: 1-888-4ENBREL (1-888-436-2735).

495  
496  
497  
498



499 **Wyeth<sup>®</sup>**

500 **Manufactured by:**  
501 Immunex Corporation,  
502 Thousand Oaks, CA 91320-1799  
503 Marketed by Amgen and Wyeth Pharmaceuticals

504  
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**ENBREL<sup>®</sup>**  
**(etanercept)**  
*Single-use Prefilled Syringe*  
**PATIENT INFORMATION**

8 **ENBREL<sup>®</sup>** (pronounced en-brel)

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

14 **What is ENBREL<sup>®</sup>?**

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

24 **How does ENBREL<sup>®</sup> work?**

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

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

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**Pregnancy Registry Update; 6/1/05**

1

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

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

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

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

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

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

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

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

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

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93 **What are other possible side effects with ENBREL®?**

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

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96 **Who should not take ENBREL®?**

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

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

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

102 **Pregnancy Registry:** Amgen has developed a registry for pregnant women exposed to  
103 ENBREL®. The purpose of this registry is to check the health of the pregnant mother and

104 her child. Patients are encouraged to contact the registry themselves or ask their doctors  
105 to contact the registry for them by calling 1-877-311-8972.

106 **Can I take ENBREL<sup>®</sup> if I am taking other medicines for my Rheumatoid**  
107 **Arthritis, Psoriasis, Psoriatic Arthritis, Ankylosing Spondylitis or other**  
108 **conditions?**

109 Yes, you can take other medicines if your doctor has prescribed them or has told you it is  
110 OK to take them while you are taking ENBREL<sup>®</sup>. It is important that you tell your doctor  
111 about any other medicines (for example, high blood pressure medicine) you are taking for  
112 other conditions before you start taking ENBREL<sup>®</sup>. Taking ENBREL<sup>®</sup> with Kineret<sup>®</sup>  
113 (anakinra) is not recommended because this may increase your risk of getting a serious  
114 infection.

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

117 **How do I take ENBREL<sup>®</sup>?**

118 ENBREL<sup>®</sup> is given by injection under the skin.

119 Make sure you have been shown how to inject ENBREL<sup>®</sup> before you do it yourself. You  
120 can call your doctor or the ENBREL<sup>®</sup> toll-free information line at 1-888-4ENBREL<sup>®</sup>  
121 (1-888-436-2735) if you have any questions about ENBREL<sup>®</sup> or about giving yourself an  
122 injection. Someone you know can also help you with your injection. Remember to take  
123 this medicine just as your doctor has told you and do not miss any doses.

124 **Adults**

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

127 If you have psoriasis, the recommended starting dose of ENBREL<sup>®</sup> for adult patients is a  
128 50 mg dose twice a week (3 or 4 days apart) given for three months. After 3 months, your  
129 doctor will tell you to reduce your dose to 50 mg once per week. The 50 mg dose of  
130 ENBREL<sup>®</sup> can be given as one injection using a single-use prefilled syringe.

131 **Children**

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

136 **What should I do if I miss a dose of ENBREL®?**

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

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

140 **STEP 1: Setting Up for an Injection**

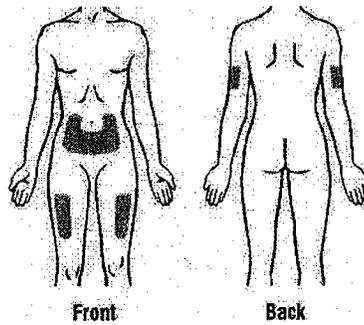
- 141 1. Select a clean, well-lit, flat work surface, such as a table.
- 142 2. Take the ENBREL® carton containing the prefilled syringes out of the refrigerator and  
143 place it on your flat work surface. Remove one prefilled syringe and place it on your  
144 work surface. Do not shake the prefilled syringe of ENBREL®. Place the carton  
145 containing any remaining prefilled syringes back into the refrigerator (2° to 8°C (36°  
146 to 46°F)). If you have any questions about storage, contact your doctor, nurse, or  
147 pharmacist for further instructions.
- 148 3. Check the expiration date on the prefilled syringe. If the expiration date has passed,  
149 do not use the prefilled syringe and contact your pharmacist or call 1-888-4ENBREL  
150 (1-888-436-2735) for assistance.
- 151 4. Wait 15 to 30 minutes to allow the ENBREL® in the prefilled syringe to reach room  
152 temperature. **DO NOT** remove the needle cover while allowing it to reach room  
153 temperature. Do not warm ENBREL® in any other way (for example, do not warm it  
154 in a microwave or in hot water).
- 155 5. Assemble the additional supplies you will need for your injection. These include an  
156 alcohol swab, a cotton ball or gauze, and a puncture-resistant disposal container.
- 157 6. Wash your hands with soap and warm water.
- 158  
159 7. Make sure the solution in the prefilled syringe is clear and colorless. **Do not inject**  
160 **the solution if it is discolored, contains lumps, flakes, or particles.** If the solution  
161 in the prefilled syringe is not clear and colorless, or contains particles; contact your  
162 pharmacist or call 1-888-4ENBREL (1-888-436-2735) for assistance.

163 **STEP 2: Choosing and Preparing an Injection Site**

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

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- 169 2. Rotate the site for each injection. Do not inject into areas where the skin is tender,  
170 bruised, red, or hard. Avoid areas with scars or stretch marks.
- 171 3. If you have psoriasis, you should try not to inject directly into any raised, thick, red, or  
172 scaly skin patches ("psoriasis skin lesions").
- 173
- 174 4. To prepare the area of skin where ENBREL<sup>®</sup> is to be injected, wipe the injection site  
175 with an alcohol swab. **Do not touch this area again before giving the injection.**

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### 177 STEP 3: Injecting ENBREL<sup>®</sup> Using a Prefilled Syringe

- 178 1. Pick up the prefilled syringe from your flat work surface. Hold the barrel of the  
179 prefilled syringe with one hand and pull the needle cover straight off.
- 180
- 181 When you remove the needle cover, there may be a drop of liquid at the end of the  
182 needle; this is normal. Do not touch the needle or allow it to touch any surface. Do  
183 not touch or bump the plunger. Doing so could cause the liquid to leak out.

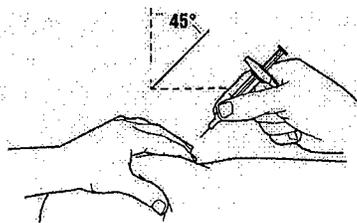
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- 184
- 185 2. Holding the syringe with the needle pointing up, check the syringe for air bubbles. If  
186 there are bubbles, gently tap the syringe with your finger until the air bubbles rise to  
187 the top of the syringe. Slowly push the plunger up to force the air bubbles out of the  
188 syringe.
- 189
- 190 3. Holding the syringe in one hand like a pencil, use the other hand to gently pinch a fold  
191 of skin at the cleaned injection site and hold it firmly.
- 192
- 193 4. Insert the needle at a slight angle (45 degrees) to the skin. With a quick, "dart-like"  
194 motion, insert the needle into the skin.
- 195

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197

198 5. After the needle is inserted, let go of the skin. Pull the plunger back slightly. If blood  
 199 comes into the syringe, do not inject ENBREL<sup>®</sup> because the needle has entered a  
 200 blood vessel. Withdraw the needle and discard it in a puncture-resistant container.  
 201 Repeat the steps to prepare for an injection using a new prefilled syringe of  
 202 ENBREL<sup>®</sup>. Do not use the same prefilled syringe.

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203 6. If no blood appears in the syringe, slowly push the plunger all the way down to inject  
 204 ENBREL<sup>®</sup>.

205 7. When the syringe is empty, pull the needle out of the skin, being careful to keep it at  
 206 the same angle as inserted. There may be a little bleeding at the injection site. You  
 207 can press a cotton ball or gauze over the injection site for 10 seconds. Do not rub the  
 208 injection site. If needed, you may cover the injection site with a bandage.  
 209

#### 210 STEP 4: Disposing of Supplies

211 • The syringe should **NEVER** be reused. **NEVER** recap a needle.

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213 • Dispose of the used syringe in a puncture-resistant container. Use a hard plastic  
 214 container with a screw top or hard plastic lid. A SHARPS container made specifically  
 215 for disposing of used syringes and needles may be used. Puncture-resistant containers  
 216 may also be purchased at your local pharmacy. **Do not** recycle the container.  
 217

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218 • Keep the container out of reach of children. When the container is about two-thirds  
 219 full, dispose of it as instructed by your healthcare provider. Follow any special state  
 220 or local laws regarding the proper disposal of needles and syringes.  
 221

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222 • Used alcohol swabs should be placed in the trash.  
 223

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224 A healthcare provider familiar with ENBREL<sup>®</sup> should answer all questions. A toll-free  
 225 information service is also available: 1-888-4ENBREL (1-888-436-2735).  
 226  
 227

228

**AMGEN**

229

**Wyeth**

230

231 **Manufactured by:**

232 Immunex Corporation,

233 Thousand Oaks, CA 91320-1799

234 Marketed by Amgen and Wyeth Pharmaceuticals

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