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

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

Physical Function Response

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

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

In Study IV, median HAQ scores improved from baseline levels of 1.8, 1.8, and 1.8 to 1.1, 1.0, and 0.6 at 12 months in the MTX, Enbrel, and Enbrel/MTX combination treatment groups, respectively (combination versus both MTX and Enbrel, $p < 0.01$). Twenty-nine percent of patients in the MTX alone treatment group had an improvement of HAQ of at least 1 unit versus 40% and 51% in the Enbrel alone and the Enbrel/MTX combination treatment groups, respectively.

Radiographic Response

In Study III, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and Joint Space Narrowing (JSN) score. Radiographs of hands/wrists and forefeet were obtained at baseline, 6 months, 12 months, and 24 months and scored by readers who were unaware of treatment group. The results are shown in Table 9. A significant difference for change in erosion score was observed at 6 months and maintained at 12 months.

**Table 9. Mean Radiographic Change Over 6 and 12 Months in Study III**

| | | MTX | 25 mg Enbrel | MTX/Enbrel (95% Confidence Interval*) | P Value |
|---|---|---|---|---|---|
| 12 Months | Total Sharp Score | 1.59 | 1.00 | 0.59 (-0.12, 1.30) | 0.1 |
| | Erosion Score | 1.03 | 0.47 | 0.56 (0.11, 1.00) | 0.002 |
| | JSN Score | 0.56 | 0.52 | 0.04 (-0.39, 0.46) | 0.5 |
| 6 Months | Total Sharp Score | 1.06 | 0.57 | 0.49 (0.06, 0.91) | 0.001 |
| | Erosion Score | 0.68 | 0.30 | 0.38 (0.09, 0.66) | 0.001 |
| | JSN Score | 0.38 | 0.27 | 0.11 (-0.14, 0.35) | 0.6 |

* 95% confidence intervals for the differences in change scores between MTX and Enbrel.

Patients continued on the therapy to which they were randomized for the second year of Study III. Seventy-two percent of patients had x-rays obtained at 24 months. Compared to the patients in the MTX group, greater inhibition

of progression in TSS and erosion score was seen in the 25 mg Enbrel group, and, in addition, less progression was noted in the JSN score.

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

In Study IV, less radiographic progression (TSS) was observed with Enbrel in combination with MTX compared with Enbrel alone or MTX alone at month 12 (Table 10). In the MTX treatment group, 55% of patients experienced no radiographic progression (TSS change ≤ 0.0) at 12 months compared to 63% and 76% in the Enbrel alone and the Enbrel/MTX combination treatment groups, respectively.

**Table 10. Mean Radiographic Change in Study IV at 12 Months (95% Confidence Interval)**

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

* Analyzed radiographic ITT population.
[a] $p < 0.05$ for comparison of Enbrel versus MTX.
[b] $p < 0.05$ for comparison of Enbrel/MTX versus MTX.
[c] $p < 0.05$ for comparison of Enbrel/MTX versus Enbrel.

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

### 14.2 Polyarticular Juvenile Idiopathic Arthritis (JIA)

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

In part 1 of the study, 51 of 69 (74%) patients demonstrated a clinical response and entered part 2. In part 2, 6 of 25 (24%) patients remaining on Enbrel experienced a disease flare compared to 20 of 26 (77%) patients receiving placebo ($p = 0.007$). From the start of part 2, the median time to flare was ≥ 116 days for patients who received Enbrel and 28 days for patients who received placebo. Each component of the JIA core set criteria worsened in the arm that received placebo and remained stable or improved in the arm that continued on Enbrel. The data suggested the possibility of a higher flare rate among those patients with a higher baseline ESR. Of patients who demonstrated

a clinical response at 90 days and entered part 2 of the study, some of the patients remaining on Enbrel continued to improve from month 3 through month 7, while those who received placebo did not improve.

The majority of JIA patients who developed a disease flare in part 2 and reintroduced Enbrel treatment up to 4 months after discontinuation re-responded to Enbrel therapy in open-label studies. Most of the responding patients who continued Enbrel therapy without interruption have maintained responses for up to 48 months.

Studies have not been done in patients with polyarticular JIA to assess the effects of continued Enbrel therapy in patients who do not respond within 3 months of initiating Enbrel therapy, or to assess the combination of Enbrel with MTX.

### 14.3 Psoriatic Arthritis

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

Compared to placebo, treatment with Enbrel resulted in significant improvements in measures of disease activity (Table 11).

**Table 11. Components of Disease Activity in Psoriatic Arthritis**

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

[a] $p < 0.001$ for all comparisons between Enbrel and placebo at 6 months.
[b] Scale 0-78.
[c] Scale 0-76.
[d] Likert scale: 0 = best; 5 = worst.
[e] Health Assessment Questionnaire: 0 = best; 3 = worst; includes eight categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.
[f] Normal range: 0-0.79 mg/dL.

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

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

Radiographic Response

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

Most patients showed little or no change in the modified TSS during this 24-month study (median change of 0 in both patients who initially received Enbrel or placebo). More placebo-treated patients experienced larger magnitudes of radiographic worsening (increased TSS) compared to Enbrel treatment during the controlled period of the study. At 12 months, in an exploratory analysis, 12% (12 of 104) of placebo patients compared to none of the 101 Enbrel-treated patients had increases of 3 points or more in TSS. Inhibition of radiographic progression was maintained in patients who continued on Enbrel during the second year. Of the patients with 1-year and 2-year x-rays, 3% (2 of 71) had increases of 3 points or more in TSS at 1 and 2 years.

Physical Function Response

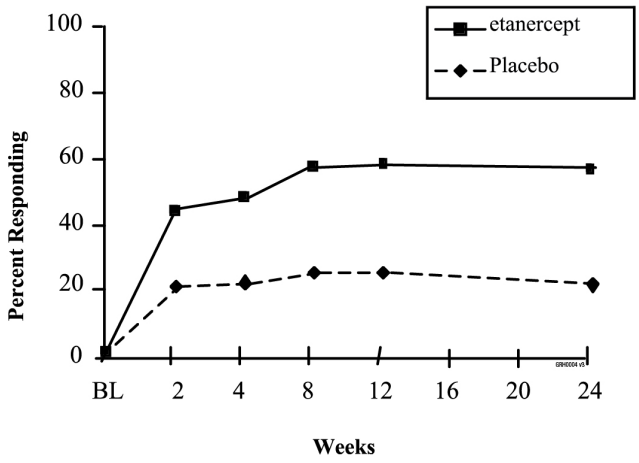
In the PsA study, physical function and disability were assessed using the HAQ Disability Index (HAQ-DI) and the SF-36 Health Survey. Patients treated with 25 mg Enbrel twice weekly showed greater improvement from baseline in the HAQ-DI score (mean decreases of 54% at both months 3 and 6) in comparison to placebo (mean decreases of 6% at both months 3 and 6) ($p < 0.001$). At months 3 and 6, patients treated with Enbrel showed greater improvement from baseline in the SF-36 physical component summary score compared to patients treated with placebo, and no worsening in the SF-36 mental component summary score. Improvements in physical function and disability measures were maintained for up to 2 years through the open-label portion of the study.

### 14.4 Ankylosing Spondylitis

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

The primary measure of efficacy was a 20% improvement in the Assessment in Ankylosing Spondylitis (ASAS) response criteria. Compared to placebo, treatment with Enbrel resulted in improvements in the ASAS and other measures of disease activity (Figure 2 and Table 12).

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




At 12 weeks, the ASAS 20/50/70 responses were achieved by 60%, 45%, and 29%, respectively, of patients receiving Enbrel, compared to 27%, 13%, and 7%, respectively, of patients receiving placebo ($p \leq 0.0001$, Enbrel versus 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 multicenter, randomized, placebo-controlled study of 84 patients with AS.

**Table 12. Components of Ankylosing Spondylitis Disease Activity**

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

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

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

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

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

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

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

### 14.5 Adult Plaque Psoriasis

The safety and efficacy of Enbrel were assessed in two randomized, double-blind, placebo-controlled studies in adults with chronic stable PsO involving ≥ 10% of the body surface area, a minimum Psoriasis Area and Severity Index (PASI) score of 10 and who had received or were candidates for systemic antipsoriatic therapy or phototherapy. Patients with guttate, erythrodermic, or pustular psoriasis and patients with severe infections within 4 weeks of screening were excluded from study. No concomitant major antipsoriatic therapies were allowed during the study.

Study I evaluated 672 subjects who received placebo or Enbrel SC at doses of 25 mg once a week, 25 mg twice a week, or 50 mg twice a week for 3 months. After 3 months, subjects continued on blinded treatments for an additional 3 months during which time subjects originally randomized to placebo began treatment with blinded Enbrel at 25 mg twice weekly (designated as placebo/Enbrel in Table 13); subjects originally randomized to Enbrel continued on the originally randomized dose (designated as Enbrel/Enbrel groups in Table 13).

Study II evaluated 611 subjects who received placebo or Enbrel SC at doses of 25 mg or 50 mg twice a week for 3 months. After 3 months of randomized, blinded treatment, subjects in all three arms began receiving open-label Enbrel at 25 mg twice weekly for 9 additional months.

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

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

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

More subjects randomized to Enbrel than placebo achieved at least a 75% reduction from baseline PASI score (PASI 75) with a dose response relationship across doses of 25 mg once a week, 25 mg twice a week and 50 mg twice a week (Tables 13 and 14). The individual components of the PASI (induration, erythema and scaling) contributed comparably to the overall treatment-associated improvement in PASI.

**Table 13. Study I Outcomes at 3 and 6 Months**

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

[a] $p = 0.001$ compared with placebo.
[b] $p < 0.0001$ compared with placebo.

**Table 14. Study II Outcomes at 3 Months**

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

[a] $p < 0.0001$ compared with placebo.

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

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

In Study I, among subjects who were PASI 75 responders at 3 months, retreatment with their original blinded Enbrel dose after discontinuation of up to 5 months resulted in a similar proportion of responders as in the initial double-blind portion of the study.

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

### 14.6 Pediatric Plaque Psoriasis

A 48-week, randomized, double-blind, placebo-controlled study enrolled 211 pediatric subjects 4 to 17 years of age, with moderate to severe plaque psoriasis (PsO) (as defined by a sPGA score ≥ 3 [moderate, marked, or severe], involving ≥ 10% of the body surface area, and a PASI score ≥ 12) who were candidates for phototherapy or systemic therapy, or were inadequately controlled on topical therapy. Subjects in all treatment groups had a median baseline PASI score of 16.4, and the percentage of subjects with baseline sPGA classifications was 65% for moderate, 31% for marked, and 3% for severe. Across all treatment groups, the percentage of subjects who previously received systemic or phototherapy for PsO was 57%.

Subjects received Enbrel 0.8 mg/kg (up to a maximum of 50 mg per dose) or placebo once weekly for the first 12 weeks. After 12 weeks, subjects entered a 24-week open-label treatment period, in which all subjects received Enbrel at the same dose. This was followed by a 12-week withdrawal-retreatment period.

Response to treatment was assessed after 12 weeks of therapy and was defined as the proportion of subjects who achieved a reduction in PASI score of at least 75% from baseline. The PASI is a composite score that takes into consideration both the fraction of body surface area affected and the nature and severity of psoriatic changes within the affected regions (induration, erythema and scaling).

Other evaluated outcomes included the proportion of subjects who achieved a score of "clear" or "almost clear" by the sPGA and the proportion of subjects with a reduction in PASI score of at least 90% from baseline. The sPGA is a 6-category scale ranging from "5 = severe" to "0 = none" indicating the physician's overall assessment of the PsO severity focusing on induration, erythema and scaling. Treatment success of "clear" or "almost clear" consisted of none or minimal elevation in plaque, up to faint red coloration in erythema and none or minimal fine scale over < 5% of the plaque.

Efficacy results are summarized in Table 15.

**Table 15. Pediatric Plaque Psoriasis Outcomes at 12 Weeks**

| | Placebo (N = 105) | Enbrel 0.8 mg/kg Once Weekly (N = 106) |
|---|---|---|
| PASI 75, n (%) | 12 (11%) | 60 (57%) |
| PASI 90, n (%) | 7 (7%) | 29 (27%) |
| sPGA "clear" or "almost clear" n (%) | 14 (13%) | 55 (52%) |

Maintenance of Response

To evaluate maintenance of response, subjects who achieved PASI 75 response at Week 36 were re-randomized to either Enbrel or placebo during a 12-week randomized withdrawal period. The maintenance of PASI 75 response was evaluated at Week 48. The proportion of subjects who maintained PASI 75 response at Week 48 was higher for subjects treated with Enbrel (65%) compared to those treated with placebo (49%).

## 15 REFERENCES


1. National Cancer Institute. Surveillance, Epidemiology, and End Results Database (SEER) Program. SEER Incidence Crude Rates, 13 Registries, 1992-2002.
2. Bröms G, Granath F, Ekbom A, et al. Low Risk of Birth Defects for Infants Whose Mothers Are Treated With Anti-Tumor Necrosis Factor Agents During Pregnancy. *Clin Gastroenterol Hepatol.* 2016;14:234-241.e5


## 16 HOW SUPPLIED/STORAGE AND HANDLING

Enbrel (etanercept) injection is supplied as a clear and colorless sterile, preservative-free solution for subcutaneous administration in single-dose prefilled syringes, an Enbrel single-dose prefilled SureClick autoinjector with a 27-gauge, ½-inch needle, or a single-dose vial. The prefilled syringe and SureClick autoinjector are not made with natural rubber latex.

Each Enbrel® Mini single-dose prefilled cartridge for use with the AutoTouch® reusable autoinjector contains 1.0 mL of 50 mg/mL of etanercept. The AutoTouch reusable autoinjector and Enbrel Mini single-dose prefilled cartridge are not made with natural rubber latex.

The AutoTouch reusable autoinjector contains no drug and must use an Enbrel Mini single-dose prefilled cartridge. In addition, the AutoTouch Connect® reusable autoinjector would allow for data connectivity via Bluetooth wireless technology.

| | | |
|---|---|---|
| **50 mg/mL** single-dose prefilled syringe | Carton of 4 | NDC 58406-435-04<br>NDC 58406-021-04 |
| **50 mg/mL** single-dose prefilled SureClick autoinjector | Carton of 4 | NDC 58406-445-04<br>NDC 58406-032-04 |
| **25 mg/0.5 mL** single-dose prefilled syringe | Carton of 4 | NDC 58406-455-04<br>NDC 58406-010-04 |
| **50 mg/mL** Enbrel Mini single-dose prefilled cartridge for use with the AutoTouch reusable autoinjector only | Cartridges: Carton of 4 | NDC 58406-456-04<br>NDC 58406-044-04 |
| | AutoTouch Reusable Autoinjector: Carton of 1 | NDC 58406-470-01 |
| | AutoTouch Connect Reusable Autoinjector:<br>Carton of 1 | NDC 58406-480-01 |
| **25 mg/0.5 mL** single-dose vial | Carton of 4 | NDC 58406-055-04 |

Enbrel should be refrigerated at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light or physical damage. Do not store Enbrel in extreme heat or cold. DO NOT SHAKE. DO NOT FREEZE.

For convenience, storage of individual single-dose prefilled syringes, SureClick autoinjectors, single-dose vials, or Enbrel Mini cartridges at room temperature at 68°F to 77°F (20°C to 25°C) for a maximum single period of 30 days is permissible, with protection from light and sources of heat. Once a single-dose prefilled syringe, SureClick autoinjector, single-dose vial, or Enbrel Mini cartridge has been stored at room temperature, it should not be placed back into the refrigerator. If not used within 30 days at room temperature, the single-dose prefilled syringe, SureClick autoinjector, single-dose vial, or Enbrel Mini cartridge should be discarded.
Do not use Enbrel beyond the expiration date stamped on the carton or barrel/cartridge label. Keep out of the reach of children.

The AutoTouch reusable autoinjector should be stored at room temperature. Do not refrigerate the AutoTouch reusable autoinjector.

**Enbrel Lyophilized Powder (Used for Weight-based Dosing)**

Enbrel (etanercept) for Injection is supplied as lyophilized powder for reconstitution in a multiple-dose vial. Each vial is supplied in a carton containing four dose trays. Each dose tray contains one 25 mg vial of etanercept lyophilized powder, one diluent syringe (1 mL Sterile Bacteriostatic Water for Injection, USP, containing 0.9%

benzyl alcohol), one 27-gauge ½-inch needle, one vial adapter, and one plunger. Each carton contains four "Mixing Date:" stickers.

| | | |
|---|---|---|
| **25 mg** multiple-dose vial | Carton of 4 | NDC 58406-425-34 |

Enbrel should be refrigerated at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light or physical damage. Do not store Enbrel in extreme heat or cold. DO NOT SHAKE. DO NOT FREEZE.

For convenience, storage of an individual dose tray containing Enbrel multiple-dose vial and diluent syringe at room temperature at 68°F to 77°F (20°C to 25°C) for a maximum single period of 14 days is permissible, with protection from light, sources of heat, and humidity. Once the dose tray has been stored at room temperature, it should not be placed back into the refrigerator. If not used within 14 days at room temperature, the dose tray should be discarded. Once a vial has been reconstituted, the solution must be used immediately or may be refrigerated for up to 14 days.

Do not use Enbrel beyond the expiration date stamped on the dose tray. Keep out of the reach of children.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling *(Medication Guide and Instructions for Use)* before the patient starts using Enbrel, and each time the prescription is renewed, as there may be new information they need to know.

Patients or their caregivers should be provided the Enbrel "Medication Guide" and provided an opportunity to read it and ask questions prior to initiation of therapy. The healthcare provider should ask the patient questions to determine any risk factors for treatment. Patients developing signs and symptoms of infection should seek medical evaluation immediately.

**Patient Counseling**

Patients should be advised of the potential benefits and risks of Enbrel. Physicians should instruct their patients to read the Medication Guide before starting Enbrel therapy and to reread each time the prescription is renewed.

Infections
Inform patients that Enbrel may lower the ability of their immune system to fight infections. Advise patients of the importance of contacting their doctor if they develop any symptoms of infection, tuberculosis or reactivation of hepatitis B virus infections.

Other Medical Conditions
Advise patients to report any signs of new or worsening medical conditions, such as central nervous system demyelinating disorders, heart failure or autoimmune disorders, such as lupus-like syndrome or autoimmune hepatitis. Counsel about the risk of lymphoma and other malignancies while receiving Enbrel. Advise patients to report any symptoms suggestive of a pancytopenia, such as bruising, bleeding, persistent fever or pallor.

Allergic Reactions
Advise patients to seek immediate medical attention if they experience any symptoms of severe allergic reactions.

**Administration of Enbrel**

If a patient or caregiver is to administer Enbrel, the patient or caregiver should be instructed in injection techniques and how to measure and administer the correct dose *[see "Instructions for Use"]*. For weight-based dosing, instruct caregivers and patients on the proper techniques for preparing, storing, measuring, and administering Enbrel solution in a single-dose vial or reconstituted lyophilized powder in a multiple-dose vial.

The first injection should be performed under the supervision of a qualified healthcare professional. The patient's or caregiver's ability to inject subcutaneously should be assessed. Patients and caregivers should be instructed in the technique, as well as proper syringe and needle disposal, and be cautioned against reuse of needles and syringes.

When using the SureClick autoinjector to administer Enbrel, the patient or caregiver should be informed that the window turns yellow when the injection is complete. After removing the autoinjector, if the window has not turned yellow, or if it looks like the medicine is still injecting, this means the patient has not received a full dose. The patient or caregiver should be advised to call their healthcare provider immediately.

When using the AutoTouch reusable autoinjector to administer Enbrel, the patient or caregiver should be informed that the status button turns green upon contact with the skin, flashes green after starting the injection, and turns off at completion of the injection. After removing the AutoTouch reusable autoinjector from the skin, if the status button has turned red, the patient or caregiver should be advised to call 1-888-4Enbrel (1-888-436-2735) immediately. If it looks like the medicine is still injecting or there is still fluid in Enbrel Mini, this means the patient has not received a full dose. The patient or caregiver should be advised to call their healthcare provider immediately.

A puncture-resistant container for disposal of needles, syringes, SureClick autoinjectors, single-dose vials, and Enbrel Mini cartridges should be used. If the product is intended for multiple use, additional syringes, needles and alcohol swabs will be required.

Patients can be advised to call 1-888-4ENBREL (1-888-436-2735) or visit www.enbrel.com for more information about Enbrel.

AMGEN®

**Enbrel® (etanercept)**

**Manufactured by:**
Immunex Corporation
Thousand Oaks, CA 91320-1799
U.S. License Number 1132

Patent: http://pat.amgen.com/enbrel/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**Medication Guide**

**Enbrel® (en-brel)**
**(etanercept)**
**injection, for subcutaneous use**

**Enbrel® (en-brel)**
**(etanercept)**
**for injection, for subcutaneous use**

Read the Medication Guide that comes with Enbrel before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or treatment. It is important to remain under your healthcare provider's care while using Enbrel.
Enbrel is a prescription medicine called a Tumor Necrosis Factor (TNF) blocker that affects your immune system.

**What is the most important information I should know about Enbrel?**
Enbrel may cause serious side effects, including:
1. Risk of Infection
2. Risk of Cancer

**1. Risk of infection**
Enbrel can lower the ability of your immune system to fight infections. Some people have serious infections while taking Enbrel. These infections include tuberculosis (TB), and infections caused by viruses, fungi, or bacteria that spread throughout their body. Some people have died from these infections.
- Your healthcare provider should test you for TB before starting Enbrel.
- Your healthcare provider should monitor you closely for symptoms of TB during treatment with Enbrel even if you tested negative for TB.
- Your healthcare provider should check you for symptoms of any type of infection before, during, and after your treatment with Enbrel.

You should not start taking Enbrel if you have any kind of infection unless your healthcare provider says it is okay.

**2. Risk of cancer**
- There have been cases of unusual cancers, some resulting in death, in children and teenagers who started using TNF-blocking agents at less than 18 years of age.
- For children, teenagers, and adults taking TNF-blocker medicines, including Enbrel, the chances of getting lymphoma or other cancers may increase.
- People with rheumatoid arthritis, especially those with very active disease, may be more likely to get lymphoma.

**Before starting Enbrel, be sure to talk to your healthcare provider:**
Enbrel may not be right for you. Before starting Enbrel, tell your healthcare provider about all of your medical conditions, including:
**Infections. Tell your healthcare provider if you:**
- have an infection. See **"What is the most important information I should know about Enbrel?"**
- are being treated for an infection.
- think you have an infection.
- have symptoms of an infection such as fever, sweats or chills, cough or flu-like symptoms, shortness of breath, blood in your phlegm, weight loss, muscle aches, warm, red or painful areas on your skin, sores on your body, diarrhea or stomach pain, burning when you urinate or urinating more often than normal, and feel very tired.
- have any open cuts on your body.
- get a lot of infections or have infections that keep coming back.
- have diabetes, HIV, or a weak immune system. People with these conditions have a higher chance for infections.
- have TB, or have been in close contact with someone with TB.
- were born in, lived in, or traveled to countries where there is a risk for getting TB. Ask your healthcare provider if you are not sure.
- live, have lived in, or traveled to certain parts of the country (such as the Ohio and Mississippi River valleys, or the Southwest) where there is a greater risk for getting certain kinds of fungal infections (histoplasmosis, coccidioidomycosis, blastomycosis). These infections may happen or become more severe if you use Enbrel. Ask your healthcare provider if you do not know if you live or have lived in an area where these infections are common.
- have or have had hepatitis B.

**Also, before starting Enbrel, tell your healthcare provider:**
- **About all the medicines you take including prescription and over-the-counter medicines, vitamins and herbal supplements including:**
  - **Orencia (abatacept) or Kineret (anakinra).** You have a higher chance for serious infections when taking Enbrel with Orencia or Kineret.
  - **Cyclophosphamide (Cytoxan).** You may have a higher chance for getting certain cancers when taking Enbrel with cyclophosphamide.
  - **Anti-diabetic medicines.** If you have diabetes and are taking medicine to control your diabetes, your healthcare provider may decide you need less anti-diabetic medicine while taking Enbrel.

Keep a list of all your medicines with you to show your healthcare provider and pharmacist each time you get a new medicine. Ask your healthcare provider if you are not sure if your medicine is one listed above.

**Other important medical information you should tell your healthcare provider before starting Enbrel, includes if you:**

- have or had a nervous system problem such as multiple sclerosis or Guillain-Barré syndrome.
- have or had heart failure.
- are scheduled to have surgery.
- have recently received or are scheduled to receive a vaccine.
  - All vaccines should be brought up-to-date before starting Enbrel.
  - People taking Enbrel should not receive live vaccines.
  - Ask your healthcare provider if you are not sure if you received a live vaccine.
- have been around someone with varicella zoster (chicken pox).
- are pregnant or plan to become pregnant. It is not known if Enbrel will harm your unborn baby. If you took Enbrel during pregnancy, talk to your healthcare provider prior to administration of live vaccines to your infant.
- are breastfeeding or plan to breastfeed. Enbrel can pass into breast milk. Talk to your healthcare provider about the best way to feed your baby while taking Enbrel.

See the section **"What are the possible side effects of Enbrel?"** below for more information.

**What is Enbrel?**

Enbrel is a prescription medicine called a Tumor Necrosis Factor (TNF) blocker.

Enbrel is used to treat:

- **moderately to severely active rheumatoid arthritis (RA).** Enbrel can be used alone or with a medicine called methotrexate.
- **moderately to severely active polyarticular juvenile idiopathic arthritis (pJIA) in children 2 years of age or older.**
- **psoriatic arthritis (PsA) in adults.** Enbrel can be used alone or with methotrexate.
- **active juvenile psoriatic arthritis (JPsA) in children 2 years of age or older.**
- **ankylosing spondylitis (AS).**
- **chronic moderate to severe plaque psoriasis (PsO) in children 4 years of age or older and adults** who may benefit from taking injections or pills (systemic therapy) or phototherapy (ultraviolet light).

You may continue to use other medicines that help treat your condition while taking Enbrel, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and prescription steroids, as recommended by your healthcare provider.

Enbrel can help reduce joint damage and the signs and symptoms of the above-mentioned diseases. People with these diseases have too much of a protein called tumor necrosis factor (TNF), which is made by your immune system. Enbrel can reduce the effect of TNF in the body and block the damage that too much TNF can cause, but it can also lower the ability of your immune system to fight infections. See **"What is the most important information I should know about Enbrel?"** and **"What are the possible side effects of Enbrel?"**

**Who should not use Enbrel?**

**Do not use Enbrel if you:**

- have an infection that has spread through your body (sepsis).

**How should I use Enbrel?**

- Enbrel is given as an injection under the skin (subcutaneous or SC).
- If your healthcare provider decides that you or a caregiver can give the injections of Enbrel at home, you or your caregiver should receive training on the right way to prepare and inject Enbrel. Do not try to inject Enbrel until you have been shown the right way by your healthcare provider or nurse.
- Enbrel is available in the forms listed below. Your healthcare provider will prescribe the type that is best for you.
  - Single-dose Prefilled Syringe
  - Single-dose Prefilled SureClick Autoinjector
  - Single-dose Vial
  - Multiple-dose Vial
  - Enbrel Mini single-dose cartridge for use with the AutoTouch reusable autoinjector
- See the detailed Instructions for Use with this Medication Guide for instructions about the right way to store, prepare, and give your Enbrel injections at home.
- Your healthcare provider will tell you how often you should use Enbrel. Do not miss any doses of Enbrel. If you forget to use Enbrel, inject your dose as soon as you remember. Then, take your next dose at your regular(ly)

scheduled time. In case you are not sure when to inject Enbrel, call your healthcare provider or pharmacist. **Do not use Enbrel more often than as directed by your healthcare provider.**

- Your child's dose of Enbrel depends on his or her weight. Your child's healthcare provider will tell you which form of Enbrel to use and how much to give your child.

**What are the possible side effects of Enbrel?**

**Enbrel can cause serious side effects, including:**

- **See "What is the most important information I should know about Enbrel?"**
- **Infections.** Enbrel can make you more likely to get infections or make any infection that you have worse. Call your healthcare provider right away if you have any symptoms of an infection. See **"Before starting Enbrel, be sure to talk to your healthcare provider"** for a list of symptoms of infection.
- **Previous Hepatitis B infection.** If you have been previously infected with the hepatitis B virus (a virus that affects the liver), the virus can become active while you use Enbrel. Your healthcare provider may do a blood test before you start treatment with Enbrel and while you use Enbrel.
- **Nervous system problems.** Rarely, people who use TNF-blocker medicines have developed nervous system problems such as multiple sclerosis, seizures, or inflammation of the nerves of the eyes. Tell your healthcare provider right away if you get any of these symptoms: numbness or tingling in any part of your body, vision changes, weakness in your arms and legs, and dizziness.
- **Blood problems.** Low blood counts have been seen with other TNF-blocker medicines. Your body may not make enough of the blood cells that help fight infections or help stop bleeding. Symptoms include fever, bruising or bleeding very easily, or looking pale.
- **New heart failure or worsening of heart failure you already have.** New or worse heart failure can happen in people who use TNF-blocker medicines like Enbrel. If you have heart failure your condition should be watched closely while you take Enbrel. Call your healthcare provider right away if you get new or worsening symptoms of heart failure while taking Enbrel, such as shortness of breath or swelling of your lower legs or feet.
- **Psoriasis.** Some people using Enbrel developed new psoriasis or worsening of psoriasis they already had. Tell your healthcare provider if you develop red scaly patches or raised bumps that may be filled with pus. Your healthcare provider may decide to stop your treatment with Enbrel.
- **Allergic reactions.** Allergic reactions can happen to people who use TNF-blocker medicines. Call your healthcare provider right away if you have any symptoms of an allergic reaction. Symptoms of an allergic reaction include a severe rash, a swollen face, or trouble breathing.
- **Autoimmune reactions, including:**
  - **Lupus-like syndrome.** Symptoms include a rash on your face and arms that gets worse in the sun. Tell your healthcare provider if you have this symptom. Symptoms may go away when you stop using Enbrel.
  - **Autoimmune hepatitis.** Liver problems can happen in people who use TNF-blocker medicines, including Enbrel. These problems can lead to liver failure and death. Call your healthcare provider right away if you have any of these symptoms: feel very tired, skin or eyes look yellow, poor appetite or vomiting, pain on the right side of your stomach (abdomen).

**Common side effects of Enbrel include:**

- **Injection site reactions** such as redness, itching, pain, swelling, bleeding or bruising. These symptoms usually go away within 3 to 5 days. If you have pain, redness, or swelling around the injection site that does not go away or gets worse, call your healthcare provider.
- **Upper respiratory infections** (sinus infections).

These are not all the side effects with Enbrel. Tell your healthcare provider about any side effect that bothers you or does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store Enbrel?**

- Store Enbrel in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Store Enbrel in the original carton to protect from light or damage.
- If needed, you may store your dose tray for the multiple-dose vial at room temperature between 68°F to 77°F (20°C to 25°C) for up to 14 days.
  - When the dose tray has reached room temperature, do not put it back in the refrigerator.
  - Throw away the dose tray that has been stored at room temperature after 14 days.
- Mixed Enbrel multiple-dose vials should be used right away or kept in the refrigerator between 36°F to 46°F (2°C to 8°C) for up to 14 days.
- If needed, you may store the Enbrel prefilled syringe, SureClick autoinjector, single-dose vial, or Enbrel Mini cartridge at room temperature between 68°F to 77°F (20°C to 25°C) for up to 30 days.
  - When Enbrel has reached room temperature, do not put it back in the refrigerator.
  - Throw away Enbrel that has been stored at room temperature after 30 days.

- **Do not** store Enbrel in extreme heat or cold such as in your vehicle's glove box or trunk.
- **Do not shake.**
- **Do not freeze.**
- **Keep Enbrel and all medicines out of the reach of children.**

**General information about the safe and effective use of Enbrel.**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Enbrel for a condition for which it was not prescribed. Do not give Enbrel to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Enbrel. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Enbrel that was written for health professionals.

**What are the ingredients in Enbrel?**

**Single-dose Prefilled Syringe, Single-dose Prefilled SureClick Autoinjector, Single-dose Vial and Enbrel Mini single-dose cartridge:**
**Active Ingredient:** etanercept
**Inactive Ingredients:** L-arginine hydrochloride, sodium chloride, and sucrose

**Multiple-dose Vial:**
**Active Ingredient:** etanercept
**Inactive Ingredients:** mannitol, sucrose, tromethamine

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Manufactured by: Immunex Corporation, Thousand Oaks, CA 91320-1799, U.S. License Number 1132

For more information, call 1 888 4ENBREL (1 888 436 2735) or www.enbrel.com.

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