Attachment 1: Product information for AusPAR etanercept (rch) Enbrel Pfizer PM-2012-04135-1-3 Date of Finalisation 24 April 2014. This Product Information was approved at the time this AusPAR was published.

PRODUCT INFORMATION

ENBREL® Etanercept (rch)

NAME OF THE MEDICINE

ENBREL (Etanercept) 25 mg and 50 mg* powder for injection and water for injections

ENBREL (Etanercept) 25 mg* and 50 mg solution for injection in pre-filled syringe

ENBREL (Etanercept) 50 mg solution for injection in Auto-injector

* not marketed

DESCRIPTION

Etanercept is a human tumour necrosis factor receptor p75 Fc fusion protein produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian expression system. Etanercept is a dimer of a protein genetically engineered by fusing the extracellular ligand binding domain of human tumour necrosis factor receptor-2 (TNFR2/p75) to the Fc domain of human IgG1. This Fc component contains the hinge, CH_2 and CH_3 regions but not the CH_1 region of IgG1. Etanercept contains 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons. Etanercept is now manufactured using a serum-free process.

The potency is determined by measuring the ability of etanercept to neutralise the TNFα-mediated growth inhibition of A375 cells. The specific activity of etanercept is 1.7×10^6 units/mg.

Powder for solution for injection (powder and solvent for solution for injection). Following reconstitution with water for injections, ENBREL is a clear colourless solution, with a pH of 7.1-7.7. ENBREL powder for injection also contains mannitol, sucrose and trometamol as excipients.

ENBREL solution for injection in the pre-filled syringe and in the Auto-injector is a clear, colourless or pale yellow solution with a pH of 6.1-6.5. ENBREL solution for injection also contains sucrose, sodium chloride, L-arginine hydrochloride, sodium phosphate-monobasic dihydrate, sodium phosphate-dibasic dihydrate and water.

PHARMACOLOGY

Pharmacodynamics

Etanercept binds specifically to tumour necrosis factor (TNF) and blocks its interaction with cell surface TNF receptors. Etanercept did not induce complement-mediated cytolysis of murine T cells that expressed TNF on the cell surface. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. TNF is a dominant cytokine in the inflammatory process of rheumatoid arthritis. Elevated levels of TNF are also found in the synovium and psoriatic plaques of patients with psoriatic arthritis and in serum and synovial tissue of patients with ankylosing spondylitis. In plaque psoriasis, infiltration by inflammatory cells including T-cells leads to increased TNF levels in psoriatic lesions, compared with levels in uninvolved skin.

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

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

Mechanism of action

Pro-inflammatory molecules that are linked in a network controlled by TNF mediate much of the joint pathology in rheumatoid arthritis and ankylosing spondylitis and skin pathology in plaque psoriasis. The mechanism of action of etanercept is thought to be its competitive inhibition of TNF binding to cell surface TNFR, preventing TNF-mediated cellular responses by rendering TNF biologically inactive. Etanercept may also modulate biological responses controlled by additional downstream molecules (e.g., cytokines, adhesion molecules, or proteinases) that are induced or regulated by TNF.

Pharmacokinetics

Absorption

Etanercept is slowly absorbed from the site of subcutaneous (SC) injection, reaching maximum concentration between 24 and 96 hours after a single dose. The absolute bioavailability is 76% as calculated in a population pharmacokinetic analysis of several studies. With twice weekly doses, it is anticipated that steady-state concentrations may be two to five-fold greater than those observed after single doses. After a single SC dose of 25 mg ENBREL, the average maximum serum concentration observed in healthy volunteers was 1.65 ± 0.66 mg/L, and area under the curve was 235 ± 96.6 mg.hr/L. Dose proportionality has not been formally evaluated, but there is no apparent saturation of clearance across the dosing range.

Distribution

A bi-exponential curve is required to describe the concentration time curve of etanercept. The central volume of distribution of etanercept is 7.6 L, while the volume of distribution at steady state is 10.4 L.

After continued dosing of RA patients (n = 25) with ENBREL for 6 months with 25 mg twice weekly, the median observed level was 3.0 mg/L (range 1.7 to 5.6 mg/L).

Excretion

Etanercept is cleared slowly from the body. The half-life is approximately 80 hours. Clearance is approximately 0.066 L/hr in patients with RA, somewhat lower than the value of 0.11 L/hr observed in healthy volunteers. Additionally, the pharmacokinetics of etanercept in rheumatoid arthritis patients, plaque psoriasis and ankylosing spondylitis patients are similar.

Serum concentration profiles at steady state were comparable among patients with RA treated with 50 mg ENBREL powder for injection once weekly and those treated with 25 mg ENBREL powder for injection twice weekly. A single 50 mg/mL injection of ENBREL was also found to be bioequivalent to two simultaneous injections of 25 mg/mL. The mean (± standard deviation) Cmax,

Cmin and partial AUC were 2.4 ± 1.5 mg/L, 1.2 ± 0.7 mg/L and 297 ± 166 mg.h/L, respectively, for patients treated with 50 mg ENBREL once weekly (n = 21); and 2.6 ± 1.2 mg/L, 1.4 ± 0.7 mg/L and 316 ± 135 mg.h/L for patients treated with 25 mg ENBREL twice weekly (n = 16). Serum concentrations in patients with RA have not been measured for periods of dosing that exceed 6 months. In an open-label, single-dose, two treatment crossover study in healthy volunteers, etanercept administered as a single injection of ENBREL 50 mg solution for injection was found to be bioequivalent to two simultaneous injections of ENBREL 25 mg powder for injection. The mean (± standard deviation) Cmax and AUC(0-T) are expressed in the table below.

	AUC_{0-t} (mg.h/L)	Cmax (mg/L)
1 x 50 mg solution SC (n=33)	535 ±192	3.90 ±1.49
2 x 25 mg powder SC (n=33)	590 ±208	4.09 ±1.65
Point Estimate (%) 90% CI	91.3 (80.9, 103.1)	96.8 (84.1, 111.3)

Although there is elimination of radioactivity in urine after administration of radiolabelled etanercept to patients and volunteers, increased etanercept concentrations were not observed in patients with acute renal or hepatic failure. The presence of renal and hepatic impairment should not require a change in dosage. There is no apparent pharmacokinetic difference between men and women.

No formal pharmacokinetic studies have been conducted to examine the metabolism of etanercept or the effects of renal or hepatic impairment. Methotrexate has no effect on the pharmacokinetics of etanercept. The effect of ENBREL on the human pharmacokinetics of methotrexate has not been investigated.

The data described above were derived from studies using etanercept manufactured using a serum-based process.

Special populations

Elderly (>65 years)

The impact of advanced age was studied in the population pharmacokinetic analysis of etanercept serum concentrations. Clearance and volume estimates in patients aged 65 to 87 years were similar to estimates in patients less than 65 years of age.

Patients with juvenile idiopathic arthritis

In a polyarticular juvenile idiopathic arthritis (JIA) trial with ENBREL, 69 patients (age 4 to 17 years) were administered 0.4 mg ENBREL/kg twice weekly for three months. Serum concentration profiles were similar to those seen in adult rheumatoid arthritis patients. The youngest children (4 years of age) had reduced clearance (increased clearance when normalised by weight) compared with older children (12 years of age) and adults. Simulation of dosing suggests that while older children (10-17 years of age) will have serum levels close to those seen in adults, younger children will have appreciably lower levels.

Paediatric patients with plaque psoriasis

Patients with paediatric plaque psoriasis (aged 4 to 17 years) were administered 0.8 mg/kg (up to a maximum dose of 50 mg per week) of etanercept once weekly for up to 48 weeks. The mean serum steady state trough concentrations ranged from 1.6 to 2.1 mg/L at weeks 12, 24, and 48. These

mean concentrations in patients with paediatric plaque psoriasis were similar to the concentrations observed in patients with juvenile idiopathic arthritis (treated with 0.4 mg/kg etanercept twice weekly, up to maximum dose of 50 mg per week). These mean concentrations were similar to those seen in adult patients with plaque psoriasis treated with 25 mg etanercept twice weekly.

CLINICAL TRIALS

This section presents data from 5 randomised controlled studies in adults with rheumatoid arthritis, 3 studies in paediatric patients with JIA, 2 studies in adults with ankylosing spondylitis, 1 study in adults with psoriatic arthritis, 2 studies in adults with plaque psoriasis and 1 study in paediatric patients with plaque psoriasis.

Adult rheumatoid arthritis

Placebo-controlled studies

The efficacy of ENBREL was assessed in a randomised, double-blind, placebo-controlled study. The study evaluated 234 adult patients with active rheumatoid arthritis who had failed therapy with at least one but no more than four disease-modifying antirheumatic drugs (DMARDs). Doses of 10 mg or 25 mg ENBREL or placebo were administered subcutaneously twice a week for 6 consecutive months. The results of this controlled trial were expressed in percentage improvement in rheumatoid arthritis using American College of Rheumatology (ACR) response criteria. The primary endpoint was achievement of an ACR 20 response at month 3. Subjects who failed to respond based on pre-specified criteria for lack of efficacy before month 3 were allowed to drop out early and were considered treatment failures. ACR 20 and 50 responses were higher in patients treated with ENBREL at 3 and 6 months than in patients treated with placebo, at all time points as seen in the table below.

ACR Responses (% of patients)

Response	Placebo (n=80)	ENBREL[a] (n=78)
ACR 20		
Month 3	23	62 [b]
Month 6	11	59 [b]
ACR 50		
Month 3	8	41 [b]
Month 6	5	40 [b]

a: 25 mg ENBREL SC twice weekly.

b: $p \leq 0.01$, ENBREL vs. placebo.

Approximately 15% of subjects who received ENBREL achieved an ACR 70 response at month 3 and month 6 compared to fewer than 5% of subjects in the placebo arm. Among patients receiving ENBREL, the clinical responses generally appeared within 1 to 2 weeks after initiation of therapy and nearly always occurred by 3 months. A dose response was seen; results with 10 mg were intermediate between placebo and 25 mg. ENBREL was significantly better than placebo in all components of the ACR criteria as well as other measures of rheumatoid arthritis disease activity not included in the ACR response criteria, such as morning stiffness. A Health Assessment Questionnaire (HAQ), which included disability, vitality, mental health, general health status and

arthritis-associated health status sub-domains, was administered every 3 months during the trial. All sub-domains of the HAQ were improved in patients treated with ENBREL compared to controls at 3 and 6 months.

After discontinuation of ENBREL, symptoms of arthritis generally returned within a month. Reintroduction of treatment with ENBREL after discontinuations of up to 24 months resulted in the same magnitudes of response as patients who received ENBREL without interruption of therapy based on results of open-label studies. Continued durable responses have been seen in open-label extension treatment trials when patients received ENBREL without interruption.

A second randomised, double-blind, placebo-controlled study also compared the safety and efficacy of ENBREL (25 mg) against placebo (SC, twice a week over 6 months) in 89 RA patients in addition to a stable dose of methotrexate. The ACR response criteria were used to assess efficacy. The primary endpoint was achievement of an ACR 20 response at 6 months. Responses were higher in patients treated with ENBREL at 3 and 6 months. Clinical responses in ENBREL-treated patients generally appeared after 1-2 weeks of therapy. In addition, approximately 15% of ENBREL-treated patients achieved an ACR 70 response at month 3 and month 6, compared to less than 5% of subjects in the placebo arm. ENBREL-treated patients experienced significantly greater improvements in all components of the ACR criteria, compared to patients in the placebo arm.

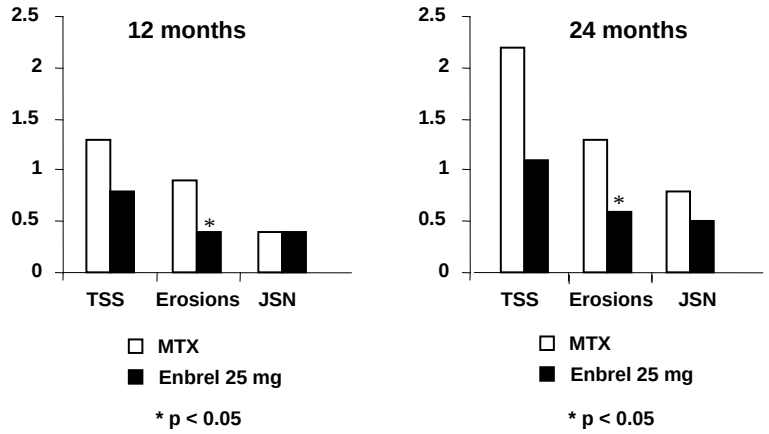
The safety and efficacy of 50 mg ENBREL (two 25 mg SC injections) administered once weekly were evaluated in a double-blind, placebo-controlled study of 420 patients with active RA. In this study, 53 patients received placebo, 214 patients received 50 mg ENBREL once weekly and 153 patients received 25 mg ENBREL twice weekly. The safety and efficacy profiles of the two ENBREL treatment regimens were comparable in their effect on signs and symptoms of RA.

Active-controlled studies

A randomised, active-controlled study with blinded radiographic evaluations as a primary endpoint compared the efficacy of ENBREL to oral methotrexate in 632 adult patients with active rheumatoid arthritis (<3 years duration) who had never received treatment with methotrexate. The patients had to have >12 tender joints, >10 swollen joints and either ESR >28 mm/hr, CRP >2.0 mg/dL, or morning stiffness for >45 minutes. Patients were at high risk of erosive disease defined as being rheumatoid factor positive or having at least three erosions at baseline. Doses of 10 mg or 25 mg ENBREL were administered SC twice a week for up to 24 months. Methotrexate doses were escalated from 7.5 mg/week to a maximum of 20 mg/week over the first 8 weeks of the trial and continued for up to 24 months. Clinical improvement including onset of action within 2 weeks with ENBREL 25 mg was similar to that seen in the previous 2 trials and was maintained for up to 24 months. At baseline, patients had a moderate degree of disability, with mean HAQ scores of 1.4 to 1.5. Treatment with ENBREL 25 mg resulted in substantial improvement at 12 months, with about 44% of patients achieving a normal HAQ score (less than 0.5). This benefit was maintained in Year 2 of this study.

In this study, 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 score (JSN). Radiographs of hands/wrists and feet were read at baseline and 6, 12 and 24 months. The 10 mg ENBREL dose had consistently less effect on structural damage than the 25 mg dose. ENBREL 25 mg was significantly superior to methotrexate for erosion scores at both 12 and 24 months. The differences in TSS and JSN were not statistically significant between methotrexate and ENBREL 25 mg. The results are shown in the figure below.

Radiographic Progression over 24 Months



In another active-controlled, double-blind, randomised study, clinical efficacy, safety and radiographic progression in RA patients treated with ENBREL alone (25 mg twice weekly), methotrexate alone (7.5 to 20 mg weekly, median dose 20 mg) and of the combination of ENBREL and methotrexate initiated concurrently were compared in 682 adult patients with active rheumatoid arthritis of 6 months to 20 years duration (median 5 years) who had a less than satisfactory response to at least 1 DMARD other than methotrexate. Forty-three percent of patients had previously received MTX a mean of 2 years prior to the trial at a mean dose of 12.9 mg/week. Patients were excluded from this study if MTX had been discontinued for lack of efficacy or for safety considerations.

Patients in the ENBREL in combination with methotrexate therapy group had significantly higher ACR 20, ACR 50, ACR 70 responses and improvement for disease activity scores (DAS) at both 24 and 52 weeks than patients in either of the single therapy groups (results shown in table below).

Clinical Efficacy Results: Comparison of ENBREL vs. Methotrexate vs. ENBREL in Combination with Methotrexate in Patients with RA of 6 Months to 20 Years Duration

Endpoint Time Point	Methotrexate (n = 228)	ENBREL (n = 223)	ENBREL + Methotrexate (n = 231)
ACR 20 Response			
Week 24	73.7%	71.3%	81.8% †,ϕ
Week 52	75.0%	75.8%	84.8% †,ϕ
ACR 50 Response			
Week 24	40.8%	40.4%	59.3% †,ϕ
Week 52	42.5%	48.4%	69.3% †,ϕ
ACR 70 Response			
Week 24	15.4%	17.0%	35.9% †,ϕ
Week 52	18.9%	24.2%	42.9% †,ϕ

Clinical Efficacy Results: Comparison of ENBREL vs. Methotrexate vs. ENBREL in Combination with Methotrexate in Patients with RA of 6 Months to 20 Years Duration

Endpoint Time Point	Methotrexate (n = 228)	ENBREL (n = 223)	ENBREL + Methotrexate (n = 231)
DAS[a]			
Baseline score	5.5	5.7	5.5
Week 24 score	3.1	3.1	$2.5^{\dagger,\phi}$
Week 52 score	3.0	3.0	$2.3^{\dagger,\phi}$

a: Values for DAS are means.

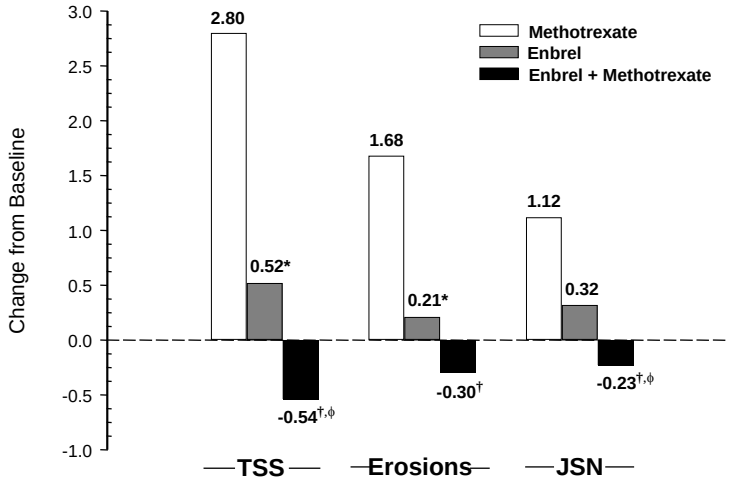
Pairwise comparison p-values: † = $p < 0.05$ for comparisons of ENBREL + methotrexate vs. methotrexate and $\phi = p < 0.05$ for comparisons of ENBREL + methotrexate vs. ENBREL

The percentage of patients who achieved low disease activity (defined as DAS < 2.4) at 52 weeks was 39%, 35% and 61% for patients in the ENBREL alone group, methotrexate alone group and the ENBREL combination group, respectively. Remission (defined as DAS < 1.6) was experienced by 18%, 14% and 37% of patients administered ENBREL alone, methotrexate alone and combination therapy respectively.

Mean HAQ scores improved from baseline levels of (1.7, 1.7 and 1.8) to (1.0, 1.1 and 0.8) at 52 weeks in the ENBREL, methotrexate and ENBREL in combination with methotrexate treatment groups, respectively (combination versus both methotrexate andENBREL, $p<0.01$).

Radiographic progression as measured by Total Sharp Score (TSS) was significantly less in the ENBREL group than in the methotrexate group at week 52. Significantly less radiographic progression (TSS) was observed with ENBREL in combination with methotrexate compared with ENBREL alone or methotrexate alone at week 52. The results for radiographic results (TSS), joint erosion and joint space narrowing (JSN) at week 52 are shown in the figure below. There was a significant decrease in TSS compared with baseline in the combination of ENBREL with methotrexate group.

Radiographic Progression: Comparison of ENBREL vs. Methotrexate vs. ENBREL in Combination with Methotrexate in Patients with RA of 6 Months to 20 Years Duration (52-Week Results)



Pairwise comparison p-values: * = $p < 0.05$ for comparisons of ENBREL vs. methotrexate, † = $p < 0.05$ for comparisons of ENBREL + methotrexate vs. methotrexate and ϕ = $p < 0.05$ for comparisons of ENBREL + methotrexate vs. ENBREL

The percentage of patients without progression (TSS change ≤ 0.5) was higher in the ENBREL in combination with methotrexate and ENBREL groups compared with methotrexate at week 24 (74%, 68% and 56%, respectively; $p<0.05$) and week 52 (80%, 68% and 57%, respectively; $p<0.05$).

Safety, efficacy and immunogenicity were assessed in an open label study of etanercept manufactured by the serum-free process (SFP) in patients with rheumatoid arthritis. Based on indirect comparisons with historical data, the results were comparable to two previous phase 3 controlled studies in subjects with RA using etanercept manufactured by a serum-based process.

Juvenile idiopathic arthritis

The safety and efficacy of ENBREL were assessed in a two-part study of 69 children with polyarticular-course juvenile idiopathic arthritis (JIA) who had a variety of JIA onset types (polyarthritis, pauciarthritis, systemic-onset). Patients aged 4 to 17 years with moderately to severely active polyarticular-course JIA refractory to or intolerant of methotrexate were enrolled; patients remained on a stable dose of a single non-steroidal 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 randomised to remain on ENBREL or receive placebo for four months and assessed for disease flare. Responses were measured using the ACR Pedi 30, defined as ≥ 30% improvement in at least three of six JIA core set criteria (active joint count, limitation of motion, physician and patient/parent global assessments, functional assessment and ESR) with no more than one variable worsening by more than 30%. Disease flare was defined as a ≥ 30% worsening in three of six JIA core set criteria and a minimum of two active joints. They could also have ≥ 30% improvement in not more than one of six JIA core set criteria.

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.

In an open-label, safety extension study, 58 paediatric patients from the above study (from the age of 4 years at time of enrolment) continued to receive ENBREL for up to 10 years. Rates of serious adverse events and serious infections did not increase with long-term exposure.

In another open-label single-arm study, 60 patients with extended oligoarthritis (15 patients aged 2 to 4, 23 patients aged 5 to 11 and 22 patients aged 12 to 17 years old), 38 patients with enthesitis-related arthritis (12 to 17 years old), and 29 patients with psoriatic arthritis (12 to 17 years old) were treated with ENBREL at a dose of 0.8 mg/kg (up to a maximum of 50 mg per dose) administered weekly for 12 weeks. In each of the JIA subtypes, the majority of patients met ACR Pedi 30 criteria and demonstrated clinical improvement in secondary endpoints such as number of tender joints and physician global assessment. The safety profile was consistent with that observed in other JIA studies.

Long-term safety of ENBREL monotherapy (n=103), ENBREL plus methotrexate (n=294), or methotrexate monotherapy (n=197) were assessed for up to 3 years in a registry of 594 children aged 2 to 18 years with juvenile idiopathic arthritis, 39 of whom were 2 to 3 years of age. Overall, infections were more commonly reported in patients treated with ENBREL compared to methotrexate alone (3.8 versus 2%), and the infections associated with ENBREL use were of a more severe nature.

Studies have not been done in patients with juvenile idiopathic arthritis to assess the effects of continued ENBREL therapy in patients who do not respond within 3 months of initiating ENBREL therapy. Additionally, studies have not been conducted to assess the effects of discontinuing or reducing the recommended dose of ENBREL following its long-term use in patients with JIA.

The long-term effects of ENBREL on the growth and development of children are not known. No formal clinical trials have been conducted in children aged 2 to 3 years. However, limited safety data from a patient registry suggest that the safety profile in children aged 2 to 3 years of age is similar to that seen in adults and children aged 4 years and older, when dosed every week with 0.8 mg/kg subcutaneously.

Adults with psoriatic arthritis

The efficacy of ENBREL was assessed in a randomised, double-blind, placebo-controlled study of 205 patients with psoriatic arthritis. Patients were between 18 and 70 years of age and had active psoriatic arthritis (≥ 3 swollen joints and ≥ 3 tender joints) in at least one of the following forms: (1) distal interphalangeal (DIP) involvement; (2) polyarticular arthritis (absence of rheumatoid nodules and presence of psoriasis); (3) arthritis mutilans; (4) asymmetric psoriatic arthritis; or (5) spondylitis-like ankylosis. Patients also had plaque psoriasis with a qualifying target lesion ≥ 2cm in diameter. Patients currently on methotrexate therapy (stable for ≥ 2 months) could continue at a stable dose of ≤25 mg/week methotrexate. Doses of 25 mg ENBREL or placebo were administered

SC twice a week for 6 months. At the end of the double-blind study, patients could enter a long-term open-label extension study for a total duration of up to 2 years.

The clinical responses were expressed as percentages of patients achieving the ACR 20, 50 and 70 response and percentages with improvement in Psoriatic Arthritis Response Criteria (PsARC). The PsARC endpoint comprises of four measures: (1) patient global assessment, (2) physician global assessment, (3) joint pain/tenderness score and (4) joint swelling score. Achievement of the PsARC endpoint requires improvement in at least two of the four measures, one of which must be joint pain/tenderness or swelling and no worsening in any of the four measures. Data have not been evaluated to establish whether ENBREL inhibits progressive joint destruction in psoriatic arthritis. Results are summarised in the Table below.

ACR and PsARC Responses of Patients with Psoriatic Arthritis in Placebo-Controlled Trial

	Percent of Patients	
	Placebo (n = 104)	ENBREL[a] (n = 101)
ACR 20		
Month 3	15	59[b]
Month 6	13	50[b]
ACR 50		
Month 3	4	38[b]
Month 6	4	37[b]
ACR 70		
Month 3	0	11[b]
Month 6	1	9[c]
PsARC		
Month 3	31	72[b]
Month 6	23	70[b]

In this study, the psoriatic skin lesions of patients with active arthritis were also improved with ENBREL treatment compared with placebo. In a subset of patients with psoriasis involvement ≥3% of body surface area, improvements in the Psoriasis Area and Severity Index (PASI) were assessed at Month 3 and Month 6. The PASI is a composite score calculated from disease activity scores and the fraction of body surface area involvement. PASI results are presented in the Table below.

PASI Responses of Patients with Psoriatic Arthritis in Placebo-Controlled Trial

	Percent of Patients	
	Placebo	ENBREL[a]
	(n = 62)	(n = 66)
PASI 50% improvement		
Month 3	15	36[c]
Month 6	18	47[b]
PASI 75% improvement		
Month 3	8	12
Month 6	3	23[c]

a: 25 mg ENBREL SC twice weekly

b: $p < 0.001$, ENBREL vs. placebo

c: $p < 0.01$, ENBREL vs. placebo

Among patients with psoriatic arthritis who received ENBREL, the clinical responses were apparent at the time of the first visit (4 weeks) and were maintained through 6 months of therapy. ENBREL was significantly better than placebo in all measures of disease activity ($p < 0.001$) and responses were similar with and without concomitant methotrexate therapy.

In this study, structural joint damage was assessed radiographically and expressed as change in modified Total Sharp Score (TSS) and its components, the erosion score and joint space narrowing score (JSN). The possible range for the modified TSS was 0 to 370. Radiographs of hands and wrists were obtained at baseline and months 6, 12 and 24.

The 1-year analyses, as shown in the table below, indicates that the difference between treatment groups was significant for mean annualized rate of change from baseline in TSS, erosion scores and for JSN. In addition, significantly more subjects in the etanercept group had no progression (≤0 change) in TSS from baseline, compared with subjects in the placebo group.

Annualised Rate of Change (Mean + SE) at 1 Year

	Placebo (n = 104)[a]	Etanercept (n = 101)[a]	p-Value
TSS	1.00 (0.29)	-0.03 (0.09)	0.0001[b]
Erosions	0.66 (0.17)	-0.09 (0.07)	0.0001[b]
JSN	0.34 (0.13)	0.05 (0.05)	0.0438[b]
Number (%) of subjects with ≤0 change in TSS	63 (61)[d]	81 (80)	0.0027[c]

Abbreviations: JSN = joint space narrowing; SE = standard error; TSS = total Sharp score.

a: Number of randomized and treatment subjects.

b: p-Values were determined using the van Elteren test with stratification for MTX use and reader pair (in the case of TSS, p was significant in the MTX and no MTX strata).

c: p-Value was determined using the Cochran-Mantel-Haenszel test with stratification for MTX use and reader pair.

d: The high placebo effect was attributed to the taking of etanercept by some patients in the overlap period following 6 months on placebo in the double-blind period.

The modified TSS at 6, 12 and 24 months are presented in the following table for those patients who entered year 2 and provided radiographs during the second year of the study.

Radiographic Progression (Mean + Standard Error Change) Annualized Change from Baseline in Total Sharp Score, Erosion and Joint Space Narrowing Scores over Time, Month 6 to Year 2[a]

	Placebo/ Etanercept (n = 70)[b]	Etanercept (n = 71)[b]
Mean (SE) change in TSS		
6 months	0.39 (0.13)	-0.33 (0.10)
1 year	0.72 (0.27)	-0.28 (0.15)
2 years	0.50 (0.24)	-0.38 (0.25)
Mean (SE) change in erosions		
6 months	0.27 (0.11)	-0.29 (0.09)
1 year	0.48 (0.20)	-0.31 (0.14)
2 years	0.23 (0.17)	-0.40 (0.18)
Mean (SE) change in JSN		
6 months	0.12 (0.06)	-0.04 (0.05)
1 year	0.24 (0.11)	0.03 (0.07)
2 years	0.27 (0.11)	0.02 (0.11)

Abbreviations: JSN = joint space narrowing; SE = standard error; TSS = total Sharp score.

a: Patients in this study were originally randomized to etanercept or to placebo.The study design included a blinded maintenance period that continued until all patients had completed at least 6 months of treatment. After the last patient completed 6 months of treatment, an open-label phase followed in which all patients received etanercept.

b: Number of randomized and treated subjects with radiograph at year 2 time point.

In subjects who received placebo during the controlled part of the study and ENBREL in the open-label part, further radiographic progression was inhibited after subjects began receivingENBREL. ENBREL treatment resulted in improvement in physical function during the double-blind period and this benefit was maintained during the longer-term exposure of up to 2 years.

Quality of life in psoriatic arthritis patients was assessed using the Health Assessment Questionnaire (HAQ) and SF-36 instruments. There was a statistically significant improvement in mean HAQ score from 1.1 to 0.5 on a scale of 0 to 3 for patients treated with ENBREL. The SF-36 showed improvements in the physical but not the mental components of the quality of life score.

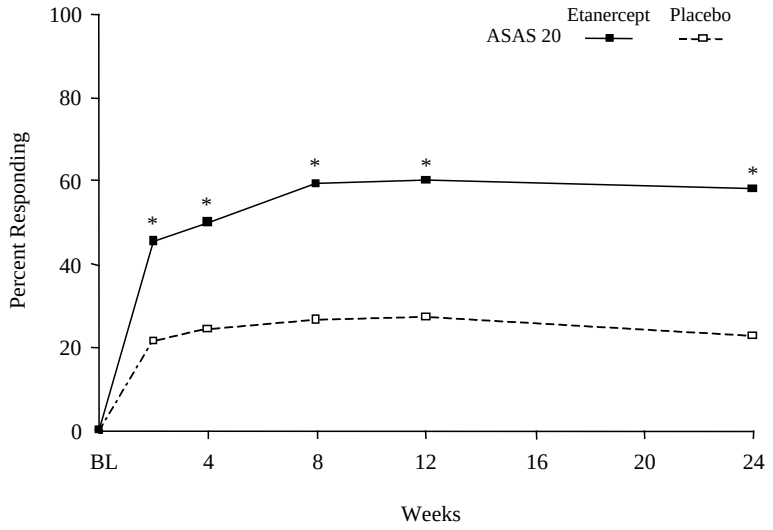
Adults with ankylosing spondylitis

The efficacy of ENBREL was assessed in 2 randomised, double-blind, placebo-controlled studies in 361 patients with ankylosing spondylitis. The largest of these trials (n = 277) enrolled patients who were between 18 and 70 years of age and had active ankylosing spondylitis as defined by the modified New York Criteria for Ankylosing Spondylitis. Patients were to have evidence of active disease based on visual analog scale (VAS) scores of ≥ 30 for average of duration and intensity of morning stiffness plus VAS scores of ≥ 30 for at least 2 of the following 3 parameters: patient global assessment; average of VAS values for nocturnal back pain and total back pain; average of

10 questions on the Bath Ankylosing Spondylitis Functional Index (BASFI). The duration of this study was up to 24 weeks and patients had a mean diagnosis of AS for 10 years. Patients with complete ankylosis of the spine were excluded from study participation. Patients taking hydroxychloroquine, sulfasalazine, methotrexate or prednisolone (≤10 mg/day) or equivalent, could continue these drugs at stable doses for the duration of the study. Doses of 25 mg of ENBREL (based on dose-finding studies in patients with rheumatoid arthritis) or placebo were administered subcutaneously twice a week for 6 months.

The primary measure of efficacy was a 20% improvement in the Assessment in Ankylosing Spondylitis (ASAS 20) response criteria. Compared to placebo, treatment with ENBREL resulted in significant improvements in clinical response as early as 2 weeks after the initiation of therapy (see figure below).

ASAS 20 Response in Patients with Ankylosing Spondylitis in a Placebo-Controlled Trial



*p < 0.001 for ENBREL vs. placebo.

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<0.001 for ENBREL vs placebo). Similar results were seen at week 24.

Components of Ankylosing Spondylitis Disease Activity

	Placebo n = 139		ENBREL [a] n = 138	
Mean 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) scale with 0 = "none" and 100 = "severe."

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

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

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

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

Adults with plaque psoriasis

The safety and efficacy of ENBREL were assessed in two randomised, double-blind, placebo-controlled studies. Study 1 evaluated 652 patients with chronic plaque psoriasis who were ≥ 18 years old, had active but clinically stable plaque psoriasis involving ≥ 10% of the body surface area and had a minimum psoriasis area and severity index (PASI) of 10 at screening. ENBREL was administered subcutaneously at doses of 25 mg once a week, 25 mg twice a week or 50 mg twice a week for 6 consecutive months. During the first 12 weeks of the double-blind treatment period, patients received placebo or one of the above three ENBREL doses. After 12 weeks of treatment, patients in the placebo group began treatment with blinded ENBREL (25 mg twice weekly); patients in the active treatment groups continued to week 24 on the dose to which they were originally randomised. This study also had a drug withdrawal period during which patients who achieved PASI improvement of at least 50% at week 24 had treatment stopped. Patients were observed off treatment for the occurrence of rebound (PASI ≥ 150% of baseline) and for the time to relapse (defined as a loss of at least half of the improvement achieved between baseline and week 24). Upon relapse, patients were retreated with ENBREL in a blinded fashion at the dose they had been receiving at week 24.

Study 2 evaluated 583 patients and had the same inclusion criteria as study 1. Patients in this study received a dose of 25 mg or 50 mg ENBREL, or placebo subcutaneously twice a week for 12 weeks and then all patients received open-label 25 mg ENBREL twice weekly for an additional 24 weeks.

The primary efficacy endpoint in both studies was the proportion of patients in each treatment group that achieved the PASI 75 (i.e., at least a 75% improvement in the PASI score from baseline) at 12 weeks. The results of the primary and secondary endpoints of both studies are shown below.

Responses of Patients with Psoriasis in Studies 1 and 2

	Study 1					Study 2		
		ENBREL					ENBREL	
	Placebo	25 mg BIW		50 mg BIW		Placebo	25 mg BIW	50 mg BIW
	n = 166	n =162	n =162	n = 164	n = 164	n = 193	n = 196	n = 196
	wk 12	wk 12	wk 24[a]	wk 12	wk 24[a]	wk 12	wk 12	wk 12
Response								
PASI 50, %	14	58*	70	74*	77	9	64*	77*
PASI 75, %	4	34*	44	49*	59	3	34*	49*
PASI 90, %	1	12*	20	22*	30	1	11*	21*
Dermatologist static global assessment, clear or almost clear, % (0 or 1 on 0-5 scale)	5	34*	39	49*	55	4	39*	57*
Percent improvement from baseline in PASI, mean	14.0	52.6*	62.1	64.2*	71.1	0.2	56.8*	67.5*
Patient global assessment of psoriasis, median (0-5 scale)	4.0	2.0*	2.0	1.5*	1.0	4.0	2.0*	1.0*
Percent improvement from baseline in Dermatology Life Quality Index, mean	10.9	50.8*	59.4	61.0*	73.8	6.2	65.4*	70.2

*$p \leq 0.0001$ compared with placebo

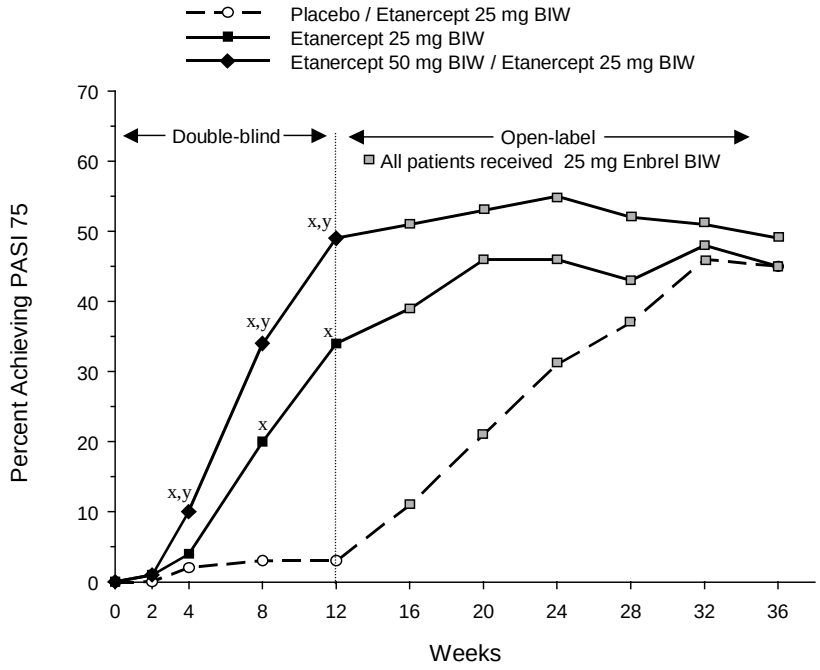
a No statistical comparisons to placebo were made at week 24 in Study 1 because the original placebo group began receiving ENBREL 25 mg BIW from week 13 to week 24.

Among patients with plaque psoriasis who received ENBREL, significant responses relative to placebo were apparent at the time of the first visit (2 weeks) for the mean percent improvement in PASI, Dermatologist Static Global Assessment of Psoriasis, Dermatology Life Quality Index and Patient Global Assessment of Psoriasis and were maintained through 24 weeks of therapy.

During the withdrawal period in study 1, symptoms of psoriasis gradually returned with a median time to disease relapse of 3 months. No rebound flare of disease and no psoriasis-related adverse events were observed. Retreatment with ENBREL resulted in a similar magnitude of response as was seen during the initial double-blind portion of the study.

At weeks 4, 8 and 12 of study 2, the 50 mg twice weekly group had a significantly higher PASI 75 response rate than the 25 mg twice weekly group ($p < 0.05$, see figure below). The majority of patients who were initially randomised to 50 mg twice weekly and had their ENBREL dose decreased at week 12 to 25 mg twice weekly maintained their PASI 75 response through week 36. For patients who received 25 mg twice weekly throughout the study, the PASI 75 response continued to improve between weeks 12 and 36.

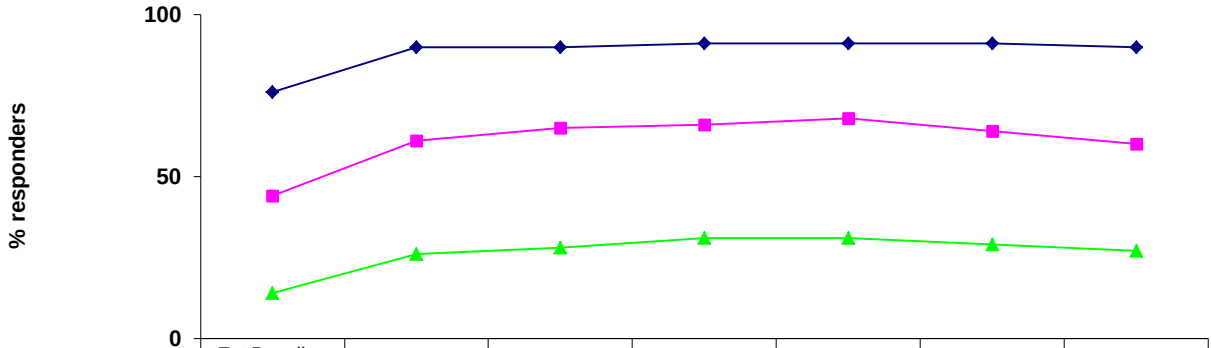
PASI 75 Response of Patients with Plaque Psoriasis in Study 2



x: = $p < 0.001$ compared with placebo, y = $p < 0.05$ for 50 mg BIW compared with 25 mg BIW.
p-values were only calculated for the double-blind period (up to week 12).

Subjects enrolled in either Study 1 or Study 2 (parent studies) were eligible to enter a phase III, open-label study to evaluate the long-term safety, tolerability, and maintenance of efficacy of ENBREL in adults with plaque PsO. During the extension study, patients in one arm received ENBREL 50 mg once weekly for 48 additional weeks (n=321).

PASI Responses of Patients with Plaque PsO Receiving ENBREL 50 mg Once Weekly in Extension Study#



	Ext Baseline (Wks since first dose)	wk 12 (60 wks)	wk 24 (72 wks)	wk 36 (84 wks)	wk 48 (96 wks)	wk 60 (108 wks)	wk 72 (120 wks)
PASI 50	76	90	90	91	91	91	90
PASI 75	44	61	65	66	68	64	60
PASI 90	14	26	28	31	31	29	27

PASI response percent responders from parent study baseline (LOCF) in patients receiving ENBREL 50 mg once weekly.

ENBREL 50 mg once-weekly continued to provide durable efficacy as demonstrated by the percentage of subjects maintaining PASI 50, 75 and 90 responses over time. It was also well tolerated in this population and its safety profile was maintained throughout the extension study.

Paediatric patients with plaque psoriasis

The efficacy of ENBREL was assessed in a randomised, double-blind, placebo-controlled study in 211 paediatric patients aged 4 to 17 years with moderate to severe plaque psoriasis (as defined by a sPGA score ≥ 3, involving ≥ 10% of the BSA, and PASI ≥ 12). Eligible patients had a history of receiving phototherapy or systemic therapy, or were inadequately controlled on topical therapy.

Patients received ENBREL 0.8 mg/kg (up to 50 mg) or placebo once weekly for 12 weeks. At week 12, more patients randomised to ENBREL had positive efficacy responses (e.g. PASI 75) than those randomised to placebo.

Paediatric Plaque Psoriasis Outcomes at 12 Weeks

	Enbrel 0.8 mg/kg Once Weekly (n = 106)	Placebo (n = 105)
PASI 75, n (%)	60 (57%)[a]	12 (11%)
PASI 50, n (%)	79 (75%)[a]	24 (23%)
sPGA “clear” or “minimal”, n (%)	56 (53%)[a]	14 (13%)

Abbreviation: sPGA-static Physician Global Assessment.

a. $p < 0.0001$ compared with placebo.

After the 12-week double-blind treatment period, all patients received ENBREL 0.8 mg/kg (up to 50 mg) once weekly for an additional 24 weeks. Responses observed during the open-label period were similar to those observed in the double-blind period.

During a randomised withdrawal period, significantly more patients re-randomised to placebo experienced disease relapse (loss of PASI 75 response) compared with patients re-randomised to ENBREL. With continued therapy, responses were maintained up to 48 weeks.

At week 12, the percent improvement in PASI scores from baseline was significantly higher in ENBREL-treated patients compared to placebo-treated patients, across all baseline disease severity subgroups (see Table below).

Percent Improvement in PASI Score at Week 12 in Different Baseline Disease Severity Subgroups

Baseline Parameter	Placebo Mean % Improvement in PASI Score (n=105)	Etanercept Mean % Improvement in PASI Score (n=106)	p-Value
PASI Score ≥10 and ≤15	25.0	67.4	<0.0001
PASI Score >15 and ≤20	11.5	60.4	<0.0001
PASI Score >20	27.2	74.8	<0.0001

This study was conducted in children with moderate or severe psoriasis. Due to the risks associated with ENBREL in children (see PRECAUTIONS), only patients with severe disease should be treated.

Immunocompetence

Evaluations of immunocompetence were performed on 49 ENBREL-treated patients with active RA. No evidence of immunosuppression was found in evaluations of delayed-type hypersensitivity skin testing, enumeration of immune effector cell populations and immunoglobulins and *in vitro* testing of neutrophil and T cell function.

Antibodies

Antibodies to ENBREL, all non-neutralising, were detected in 4 out of 96 RA patients who received ENBREL at a dose of 25 mg twice a week for up to 3 months in a placebo-controlled trial. Results from JIA patients were similar to those seen in adult RA patients treated with ENBREL. No apparent correlation of antibody development to clinical response or adverse events was seen. Of 98 patients with psoriatic arthritis who have been tested, no patient has developed antibodies to ENBREL. Among 175 ankylosing spondylitis patients treated with ENBREL, 3 patients were reported with antibodies to ENBREL, none were neutralising. In double-blind studies up to 6 months duration in plaque psoriasis, about 1% of the 1,084 patients developed antibodies to ENBREL, none were neutralising.

INDICATIONS

ENBREL is indicated for the treatment of:

Adults

Rheumatoid Arthritis

- Active, adult rheumatoid arthritis (RA) in patients who have had inadequate response to one or more disease modifying antirheumatic drugs (DMARDs). ENBREL can be used in combination with methotrexate.
- Severe, active rheumatoid arthritis in adults to slow progression of disease-associated structural damage in patients at high risk of erosive disease (see CLINICAL TRIALS).

Psoriatic Arthritis

- The signs and symptoms of active and progressive psoriatic arthritis in adults, when the response to previous disease-modifying antirheumatic therapy has been inadequate. ENBREL has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function (see CLINICAL TRIALS).

Ankylosing Spondylitis

- The signs and symptoms of active ankylosing spondylitis in adults.

Plaque Psoriasis

- Adult patients with moderate to severe chronic plaque psoriasis, who are candidates for phototherapy or systemic therapy.

Children and Adolescents

Juvenile Idiopathic Arthritis

- Active polyarthritis (rheumatoid factor positive or negative) in children and adolescents, aged 2 to 17 years, who have had an inadequate response to one or more DMARDs.††
- Active extended oligoarthritis in children and adolescents, aged 2 to 17 years, who have had an inadequate response to, or who have proved intolerant to, methotrexate.††
- Active enthesitis-related arthritis in adolescents, aged 12 to 17 years, who have had an inadequate response to, or who have proved intolerant to, conventional therapy.††
- Active psoriatic arthritis in adolescents, aged 12 to 17 years, who have had an inadequate response to, or who have proved intolerant to, methotrexate.††

ENBREL has not been studied in children aged less than 2 years.

Paediatric Plaque Psoriasis

- Chronic, severe plaque psoriasis in children and adolescents from 4 to 17 years, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. Duration of therapy to be no longer than 24 weeks and treatment to be ceased after 12 weeks if a significant PASI response is not achieved.

CONTRAINDICATIONS

1. Known hypersensitivity to etanercept or to any of its excipients.

2. Patients with, or at risk of, sepsis.

3. Treatment with ENBREL should not be initiated in patients with serious, active infection including chronic or localised infections.

4. Concurrent treatment with Interleukin-1 antagonists.

PRECAUTIONS

Infections

Patients should be evaluated for infections before, during and after treatment with ENBREL, taking into consideration that the mean elimination half-life of etanercept is 80 hours (standard deviation of 28 hours; range from 7 to 300 hours)**.**

Serious infections including sepsis and tuberculosis, have been reported with the use of ENBREL (see ADVERSE EVENTS). Some of these infections have been fatal. These infections were due to bacteria, mycobacteria, fungi, viruses and parasites (including protozoa). Opportunistic infections have also been reported (including listeriosis, legionellosis and invasive fungal infections) in patients receiving ENBREL. Many of these serious events have occurred in patients receiving concomitant medicines including immunosuppressants, or with underlying diseases that, in addition to their RA, could predispose them to infections. In some cases, fungal and other opportunistic infections are not recognised and this has resulted in delays in appropriate treatment, sometimes resulting in death. Patients who develop a new infection while undergoing treatment with ENBREL should be monitored closely. Administration of ENBREL should be discontinued if a patient develops a serious infection (e.g., tuberculosis or an atypical mycobacterial infection) or sepsis.

In evaluating patients for infections, physicians should consider the patient's risk for relevant opportunistic infections (e.g., exposure to endemic mycoses). Physicians should exercise caution when considering the use of ENBREL in patients with a history of recurring or chronic infections or with underlying conditions, which may predispose patients to infections such as advanced or poorly controlled diabetes (see CONTRAINDICATIONS). Caution should be exercised in patients at high risk of developing serious infection, including patients undergoing major surgery.

Tuberculosis

Tuberculosis (including disseminated or extrapulmonary presentation) has been observed in patients receiving TNF-blocking agents, including etanercept. Tuberculosis may be due to reactivation of latent TB infection or to new infection.

Before initiation of therapy with ENBREL, any patient at increased risk for TB should be evaluated for active or latent infection. If active TB is diagnosed, ENBREL therapy must not be initiated. Prophylaxis of latent TB infection should be initiated prior to therapy with ENBREL. Treatment of latent tuberculosis in patients with a reactive tuberculin test reduces the risk of tuberculosis reactivation in patients receiving TNF blockers.

Some patients who tested negative for latent tuberculosis prior to receiving ENBREL have developed active tuberculosis. Physicians should monitor patients receiving ENBREL for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis infection. Applicable local guidelines should be consulted. Patients with RA appear to have an increased rate of TB infection.

Cases of tuberculosis and atypical mycobacterial infections including *Mycobacterium avium* complex in patients on treatment with ENBREL have been reported. Treatment should be ceased immediately if mycobacterial infection is suspected.

All patients should be informed to seek medical advice if signs/symptoms suggestive of TB (e.g., persistent cough, wasting/weight loss, low grade fever) appear during or after ENBREL treatment.

Reactivation of hepatitis B

Reactivation of hepatitis B in patients who were previously infected with the hepatitis B virus (HBV) and had received TNF blockers, including ENBREL has been reported. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients at risk for HBV infection should be evaluated for evidence of prior HBV infection before initiating TNF blocker therapy. Prescribers should exercise caution in prescribing TNF blockers for patients previously infected with HBV. Patients who were previously infected with HBV and require treatment with TNF blockers should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. If HBV reactivation should develop in patients who are receiving ENBREL, treatment should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Worsening of hepatitis C

There have been reports of worsening of hepatitis C in patients receiving ENBREL, although a causal relationship with ENBREL has not been established.

Alcoholic hepatitis

In a study of 48 hospitalised patients treated with ENBREL or placebo for moderate to severe alcoholic hepatitis, etanercept was not efficacious and the mortality rate in pateints treated with etanercept was significantly higher after 6 months. Infections were also higher in the etanercept group. The use of etanercept in patients for the treatment of alcoholic hepatitis is not recommended. Physicians should use caution when using etanercept in patients who also have moderate to severe alcoholic hepatitis.

Hypoglycaemia in patients treated for diabetes

There have been reports of hypoglycaemia following initiation of etanercept in patients receiving medication for diabetes, necessitating a reduction in anti-diabetic medication in some of these patients.

Inflammatory bowel disease (IBD) and Uveitis in patients with juvenile idiopathic arthritis (JIA)

There have been reports of IBD in JIA patients being treated with etanercept, which is not effective for the treatment of IBD. A causal relationship with etanercept is unclear because clinical manifestations of bowel inflammation have also been observed in untreated JIA patients. There have also been reports of uveitis in JIA patients being treated with etanercept.

Concurrent administration of TNF inhibitors and anakinra

Concurrent administration of etanercept and anakinra (a recombinant, non-glycosilated form of the human Interleukin-1 receptor antagonist) has been associated with an increased risk of serious infection, an increased risk of neutropenia and no additional benefit compared to etanercept alone. The safety and efficacy of anakinra used in combination with etanercept has not been established. Therefore, combination of etanercept and anakinra is contraindicated (see also CONTRAINDICATIONS and INTERACTIONS WITH OTHER MEDICINES).

Concurrent administration of etanercept and abatacept

In clinical studies, concurrent administration of abatacept and etanercept therapy resulted in increased incidences of serious adverse events, including infections. This combination has not demonstrated increased clinical benefit; such use is not recommended (see INTERACTIONS WITH OTHER MEDICINES).

Haematological reactions

Rare cases of pancytopenia and very rare cases of aplastic anaemia, some with fatal outcome, have been reported in patients treated with ENBREL. Caution should be exercised in patients being treated with ENBREL who have a previous history of blood dyscrasias. All patients should be advised that if they develop signs and symptoms suggestive of blood dyscrasias or infections (eg, persistent fever, sore throat, bruising, bleeding, paleness) whilst on ENBREL, they should seek immediate medical advice. Such patients should be evaluated urgently, including full blood count; if any blood dyscrasias are confirmed, ENBREL should be discontinued.

Allergic reactions

Parenteral administration of any biological product should be attended by appropriate precautions in case an allergic or untoward reaction occurs. Allergic reactions associated with ENBREL administration have been reported commonly. Allergic reactions have included angioedema and urticaria. Serious reactions have occurred. If any serious allergic or anaphylactic reaction occurs, ENBREL therapy should be discontinued immediately and appropriate therapy initiated.

Latex (dry natural rubber) is present in the rubber closure of the diluent syringe (vial presentation), in the needle cover of the pre-filled syringe presentation, and also in the needle cap of the Auto-injector presentation. This may cause hypersensitivity reactions when handled by, or when ENBREL is administered to, persons with known or possible latex sensitivity. Patients or caregivers should contact their doctor before using ENBREL if these latex components will be handled by, or if ENBREL will be given to, someone with a known hypersensitivity to latex.

Congestive heart failure

There have been post-marketing reports of worsening of congestive heart failure (CHF), with and without identifiable precipitating factors, in patients taking ENBREL. There have also been rare (< 0.1%) reports of new onset CHF, including CHF in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. Two large clinical trials evaluating the use of ENBREL in the treatment of CHF were terminated early due to lack of efficacy. Although not conclusive, data from one of these trials suggests a possible tendency towards worsening CHF and higher mortality in those patients assigned to ENBREL treatment. Physicians should use caution when using ENBREL in patients who also have CHF and monitor patients carefully.

Neurologic disorders

Although no clinical trials have been performed evaluating ENBREL therapy in patients with multiple sclerosis, clinical trials of other TNF antagonists in patients with multiple sclerosis have shown increases in disease activity. Treatment with ENBREL and other agents that inhibit TNF have been associated with rare cases of new onset or exacerbation of central nervous system demyelinating disorders, some presenting with mental status changes and some associated with permanent disability. Cases of transverse myelitis, optic neuritis, multiple sclerosis, and new onset or exacerbation of seizure disorders have been observed in association with ENBREL therapy (see ADVERSE EFFECTS). Additionally, there have been very rare reports of peripheral demyelinating polyneuropathies (including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy). A careful risk/benefit evaluation, including a neurological assessment, is recommended when prescribing ENBREL therapy to patients with pre-existing or recent onset of CNS demyelinating disease, or to those who are considered to have an increased risk of developing demyelinating disease.

Use in psoriasis

There are limited data on the use of ENBREL in combination with methotrexate for the treatment of psoriasis. The safety and efficacy of this combination in psoriasis have not been established.

The safety and efficacy of ENBREL in combination with other immunosuppressive agents used in psoriasis or with phototherapy have not been studied. ENBREL should not be used in combination with such agents because of the possibility of excessive immunosuppression.

Monitoring

Based on the results of clinical studies in rheumatoid arthritis, normally no special laboratory evaluations are necessary in addition to careful medical management and supervision of patients.

Carcinogenicity

Lymphomas

TNF modulates immune responses and has a protective effect against the development of some tumours. The impact of treatment with ENBREL, on the course of development of malignancies, including those caused by immunosuppressive agents, is not understood and has not been studied. The possibility exists for anti-tumour necrosis factor (TNF) therapies, including ENBREL, to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. The impact of treatment with ENBREL on the development and course of malignancies and active and/or chronic infections is not fully understood (see ADVERSE EFFECTS). Reports of malignancies affecting various sites have been received in the post-marketing period including breast and lung carcinoma and lymphoma.

In the controlled portions of clinical trials of all the TNF blocking agents, more cases of lymphoma have been observed among patients receiving the TNF blocker compared to control patients. During the controlled portions of ENBREL trials, 3 lymphomas were observed among 4,509 ENBREL-treated patients versus 0 among 2,040 control patients (duration of controlled treatment ranged from 3 to 24 months).

Among 6,543 adult rheumatology (RA, PsA, AS) patients treated with ENBREL in controlled and uncontrolled portions of clinical trials, representing approximately 12,845 patient-years of therapy, the observed rate of lymphoma was 0.10 cases per 100 patient-years. This was 3-fold higher than the rate of lymphoma expected in the general U.S. population based on the Surveillance,

Epidemiology, and End Results (SEER) Database. While patients with rheumatoid arthritis or psoriasis, particularly those with highly active disease, may be at a higher risk (up to several fold) for the development of lymphoma, a possible risk for the development of lymphomas or other malignancies in patients treated with a TNF-antagonist cannot be excluded.

Among 4,410 adult PsO patients treated with ENBREL in clinical trials up to 36 months, representing approximately 4,278 patient-years of therapy, the observed rate of lymphoma was 0.05 cases per 100 patient-years, which is comparable to the rate in the general population. No cases were observed in ENBREL- or placebo-treated patients during the controlled portions of these trials.

Leukaemia

Cases of acute and chronic leukaemia have been reported in association with post-marketing TNF blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF blocker therapy, patients with rheumatoid arthritis may be at higher risk (approximately 2-fold) than the general population for the development of leukaemia.

During the controlled portions of ENBREL trials, 2 cases of leukaemia were observed among 5,445 (0.06 cases per 100 patient-years) ENBREL-treated patients versus 0 among 2,890 control patients (duration of controlled treatment ranged from 3 to 48 months).

Among 15,401 patients treated with ENBREL in controlled and open portions of clinical trials representing approximately 23,325 patient-years of therapy, the observed rate of leukaemia was 0.03 cases per 100 patient-years.

Other Malignancies

Information is available from 10,953 adult patients with 17,123 patient-years and 696 paediatric patients with 1,282 patient-years of experience across 45 ENBREL clinical studies.

For malignancies other than lymphoma and non-melanoma skin cancer, there was no difference in exposure adjusted rates between the ENBREL and control arms in the controlled portions of clinical studies for all indications. Analysis of the malignancy rate in combined controlled and uncontrolled portions of studies has demonstrated that types and rates are similar to what is expected in the general U.S. population based on the SEER database and suggests no increase in rates over time. Whether treatment with ENBREL might influence the development and course of malignancies in adults is unknown.

In a placebo-controlled study of 180 patients with Wegener's granulomatosis, the addition of ENBREL to standard treatment (including cyclophosphamide and high-dose steroids) was no more efficacious than standard treatment alone. The group of patients who received ENBREL experienced more non-cutaneous malignancies of various types than the patient group receiving standard treatment alone. The use of ENBREL for treatment of Wegener's granulomatosis is not recommended.

Melanoma and Non-melanoma skin cancer

Melanoma and non-melanoma skin cancer (NMSC) have been reported in patients treated with TNF-antagonists including ENBREL. Postmarketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with ENBREL. Periodic skin examination is recommended for all patients who are at increased risk for skin cancer. Combining the results of controlled portions of clinical trials of ENBREL, more cases of non-melanoma skin cancer were

observed in patients taking ENBREL compared with control patients, particularly in patients with psoriasis. Long-term animal studies have not been conducted to evaluate the carcinogenic potential of ENBREL.

Among 3,306 adult rheumatology (RA, PsA, AS) patients treated with ENBREL in controlled clinical trials representing approximately 2,669 patient-years of therapy, the observed rate of NMSC was 0.41 cases per 100 patient-years vs 0.37 cases per 100 patient-years among 1,521 control-treated patients representing 1,077 patient-years. Among 1,245 adult psoriasis patients treated with ENBREL in controlled clinical trials, representing approximately 283 patient-years of therapy, the observed rate of NMSC was 3.54 cases per 100 patient-years vs 1.28 cases per 100 patient-years among 720 control-treated patients representing 156 patient-years.

Among 15,401 patients treated with ENBREL in controlled and open portions of clinical trials representing approximately 23,325 patient-years of therapy, the observed rate of melanoma was 0.043 cases per 100 patient-years.

Immunosuppression

In a study of 49 patients with RA treated with ENBREL, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cell populations. The safety and efficacy of ENBREL, in patients with immunosuppression or chronic infections have not been evaluated.

Vaccinations

Most psoriatic patients receiving ENBREL were able to mount an effective B-cell immune response to pneumococcal polysaccharide vaccine, but titers in aggregate were moderately lower and fewer patients had two-fold rises in titers compared to patients not receiving ENBREL. Live vaccines should not be given concurrently with ENBREL (see INTERACTIONS WITH OTHER MEDICINES). No data are available on the secondary transmission of infection by live vaccines in patients receiving ENBREL. If possible, bring paediatric patients up to date with all immunisations (including varicella) in agreement with current immunisation guidelines prior to initiating ENBREL therapy. Patients with a significant exposure to varicella virus should temporarily discontinue ENBREL therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

Autoantibody formation

Treatment with ENBREL may result in the formation of autoimmune antibodies (see ADVERSE EFFECTS). Rare reports have been described in clinical trials and post-marketing experience of autoimmune hepatitis, a lupus-like syndrome or rashes compatible with subacute cutaneous lupus or discoid lupus. If a patient develops symptoms and findings suggestive of autoimmune hepatitis or a lupus-like syndrome, treatment should be discontinued and the patient carefully evaluated.

Genotoxicity

Genotoxicity studies showed no evidence of gene mutations or chromosomal damage.

Effects on fertility

Long-term animal studies have not been conducted to evaluate the effects of ENBREL on fertility.

Use in pregnancy

Category B2

The safe use of ENBREL during pregnancy has not been established. Therefore, ENBREL should be used during pregnancy only if clearly needed.

Developmental toxicity studies have been performed in rats and rabbits at doses resulting in AUC-based systemic exposure levels of etanercept that were at least 12-fold higher than in humans at the highest proposed therapeutic dose of 50 mg and have revealed no evidence of harm to the foetus due to ENBREL. There are, however, no studies in pregnant women. Animal studies are not always predictive of human response.

Etanercept crosses the placenta and has been detected in the serum of infants born to female patients treated with ENBREL during pregnancy. The clinical impact of this is unknown, however, infants may be at increased risk of infection. Administration of live vaccines to infants for 16 weeks after the mother's last dose of ENBREL is generally not recommended.

Use in lactation

The safe use of ENBREL during lactation has not been established. Etanercept has been reported to be excreted in human breast milk following subcutaneous administration. There are no animal studies assessing the effects of ENBREL on the neonate. Because of the potential for serious adverse reactions from ENBREL in nursing infants, a decision should be made whether to discontinue nursing or to discontinue ENBREL while nursing.

Paediatric use

ENBREL has not been studied in children less than 2 years of age.

Studies have not been done in patients with JIA to assess the effects of continued ENBREL therapy in patients who do not respond within 3 months of initiating ENBREL therapy. Additionally, studies have not been conducted to assess the effects of discontinuing or reducing the recommended dose of ENBREL following its long-term use in patients with JIA.

Malignancies, some fatal, have been reported among children, adolescents and young adults who received treatment with TNF-blocking agents (initiation of therapy at ≤ 18 years of age), including ENBREL to treat JIA and other indications. Approximately half of the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous post-marketing reports. These cases were derived from several sources including registries and post-marketing reports. In addition, there was one case of lymphoma reported in paediatric clinical trials.

Two JIA patients developed varicella infection and signs and symptoms of aseptic meningitis, which resolved without sequelae. Patients with a significant exposure to varicella virus should temporarily discontinue ENBREL therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

There have been reports of inflammatory bowel disease and uveitis in patients with JIA (see PRECAUTIONS-Inflammatory bowel disease (IBD) and Uveitis in patients with juvenile idiopathic arthritis (JIA)).

The long-term effects of ENBREL on the growth and development of children are not known.

Use in the elderly

A total of 480 RA patients aged 65 years or older have been studied in clinical trials. In PsO randomised clinical trials, a total of 138 out of 1,965 patients treated with ENBREL or placebo were age 65 or older. No overall differences in safety or effectiveness were observed between these patients and younger patients, but the number of geriatric PsO patients is too small to determine whether they respond differently from younger patients. Greater sensitivity of some older individuals cannot be ruled out. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

Effects on laboratory tests

No effects on laboratory tests have been reported in adults. An analysis of 54 JIA patients in an open-label study demonstrated low haemoglobin, low albumin and low lymphocyte counts in 63%, 39% and 30% of juvenile patients, respectively. These observations, however, appear to be attributed to the underlying disease, rather than treatment with ENBREL.

Effects on ability to drive and use of machines

No studies on the effects on the ability to drive and use machines have been performed.

INTERACTIONS WITH OTHER MEDICINES

Methotrexate

ENBREL may be administered in combination with methotrexate for the treatment of rheumatoid arthritis. In a safety and efficacy trial, methotrexate had no effect on the pharmacokinetics of ENBREL. The effect of ENBREL on the pharmacokinetics of methotrexate has not been investigated. Product Information for methotrexate should be consulted when ENBREL is administered with methotrexate.

Abatacept

In clinical studies, concurrent administration of abatacept and ENBREL resulted in increased incidences of serious adverse events, including infections, and did not demonstrate increased clinical benefit. Use of ENBREL with abatacept is not recommended.

Anakinra

Patients treated with ENBREL and anakinra were observed to have a higher rate of serious infection (7%) when compared with patients who were treated with ENBREL alone (0%, historical data). In addition, in a double-blind placebo-controlled trial, in patients receiving background methotrexate, patients treated with ENBREL and anakinra were observed to have a higher rate of serious infection and neutropenia than patients who were treated with ENBREL alone (see PRECAUTIONS).

Cyclophosphamide

The use of ENBREL in patients receiving concurrent cyclophosphamide therapy is not recommended (see PRECAUTIONS-Other malignancies).

Live vaccines

No safety data are available on the effects of live vaccine when used in combination with ENBREL. Live vaccines should therefore not be given concurrently with ENBREL.

Sulfasalazine

In a clinical study of patients who were receiving established doses of sulfasalazine, to which etanercept was added, patients in the combination group experienced a statistically significant decrease in mean white blood cell counts in comparison to groups treated with ENBREL or sulfasalazine alone.

Digoxin

Etanercept does not significantly affect digoxin exposure. There was a reduction in etanercept exposure in the presence of digoxin, however there was significant inter-subject variability. The clinical significance of this reduced exposure is uncertain.

Effect of Digoxin on pharmacokinetic parameters of Etanercept		
Mean (SD)	Etanercept	Etanercept + Digoxin
Cmax (μg/mL)	2.64 (1.24)	2.53 (1.93)
AUC $_{(0\text{-}t)}$ (μg/mL.h)	152 (68.7)	133 (96.3)

Warfarin

Etanercept does not significantly affect warfarin exposure. There was a slight reduction in etanercept exposure in the presence of warfarin, however there was significant inter-subject variability. The clinical significance of this reduced exposure is uncertain.

Effect of Warfarin on pharmacokinetic parameters of Etanercept		
Mean (SD)	Etanercept	Etanercept + Warfarin
Cmax (μg/mL)	3.5 (1.09)	3.09 (1.22)
AUC $_{(0\text{-}t)}$ (μg/mL.h)	180 (71.9)	160 (75.1)

Other

In clinical trials, no apparent interactions have been observed when ENBREL was administered with glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs) or analgesics.

ADVERSE EFFECTS

Injection site reactions

Patients with rheumatic diseases in controlled trials treated with ENBREL had a significantly higher incidence (37% cf. 10%) of injection site reactions (erythema and/or itching, pain, bleeding, bruising or swelling) compared with placebo-treated patients, and generally did not necessitate drug discontinuation. The frequency of injection site reactions was greatest in the first month and subsequently decreased in frequency. Mean duration was 3 to 5 days. No treatment was given for the majority of injection site reactions in the ENBREL treatment groups, and the majority of those patients who were given treatment received topical preparations such as corticosteroids, or oral antihistamines. Some patients who experienced injection site reactions also experienced reactions at

previous injection sites. In post-marketing experience, injection site bleeding and bruising have also been observed in conjunction with ENBREL therapy.

In controlled trials in patients with plaque psoriasis, approximately 13.6% of patients treated with ENBREL developed injection site reactions compared with 3.4% of placebo-treated patients during the first 12 weeks of treatment.

Infections

In placebo-controlled trials, no increase in the incidence of serious infections (fatal, life-threatening, or requiring hospitalisation or intravenous antibiotics) was observed. Serious infections occurred in 6.3% of rheumatoid arthritis patients treated with ENBREL for up to 48 months. These included abscess (at various sites), bacteraemia, bronchitis, bursitis, cellulitis, cholecystitis, diarrhoea, diverticulitis, endocarditis (suspected), gastroenteritis, hepatitis B, herpes zoster, leg ulcer, mouth infection, osteomyelitis, otitis, peritonitis, pneumonia, pyelonephritis, sepsis, septic arthritis, sinusitis, skin infection, skin ulcer, urinary tract infection, vasculitis, and wound infection. In the 2-year active-controlled study where patients were treated with either ENBREL alone, methotrexate alone or ENBREL in combination with methotrexate, the rates of serious infections were similar among the treatment groups. However, it cannot be excluded that the combination of ENBREL with methotrexate could be associated with an increase in the rate of infections.

There were no differences in rates of infection among patients treated with ENBREL and those treated with placebo for plaque psoriasis in placebo-controlled trials of up to 24 weeks duration. Serious infections experienced by ENBREL-treated patients included cellulitis, gastroenteritis, pneumonia, cholecystitis, osteomyelitis, gastritis, appendicitis, Streptococcal fasciitis, myositis, septic shock, diverticulitis and abscess. In the double-blind and open-label psoriatic arthritis trials, 1 patient reported a serious infection (pneumonia).

Serious and fatal infections have been reported during use of ENBREL; reported pathogens include bacteria, mycobacteria (including tuberculosis), viruses and fungi. Some have occurred within a few weeks after initiating treatment with ENBREL in patients who have underlying conditions (e.g., diabetes, congestive heart failure, history of active or chronic infections) in addition to their rheumatoid arthritis. ENBREL treatment may increase mortality in patients with established sepsis.

Opportunistic infections have been reported in association with ENBREL, including invasive fungal, parasitic (including protozoal) and bacterial (including Listeria and Legionella), and atypical mycobacterial infections. In a pooled data set of clinical trials, the overall incidence of opportunistic infections was 0.09% for the 15,402 subjects who received ENBREL. The exposure-adjusted rate was 0.06 events per 100 patient-years. In postmarketing experience, approximately half of all of the case reports of opportunistic infections worldwide were invasive fungal infections. The most commonly reported invasive fungal infections were Pneumocystis and Aspergillus. Invasive fungal infections accounted for more than half of the fatalities amongst patients who developed opportunistic infections. The majority of the reports with a fatal outcome were in patients with Pneumocystis pneumonia, unspecified systemic fungal infections, and aspergillosis.

Malignancies and lymphoproliferative disorders

Reports of malignancies affecting various sites have been received in the post-marketing period. The observed rates and incidences of new malignancies in clinical trials with ENBREL were similar to those expected for the population studied. Patients have been observed in clinical trials with ENBREL for over five years. Among 4,462 rheumatoid arthritis patients treated with ENBREL in clinical trials for a mean of 27 months (approximately 10,000 patient-years of therapy), 9

lymphomas were observed for a rate of 0.09 cases per 100 patient-years. This is 3-fold higher than the rate of lymphomas expected in the general population based on the Surveillance, Epidemiology and End Results Database. An increased rate of lymphoma up to several fold has been reported in the rheumatoid arthritis patient population and may be further increased in patients with more severe disease activity (see PRECAUTIONS**:** Carcinogenicity).

There have been reports of malignancies in a clinical trial of patients being treated for Wegener's granulomatosis (see PRECAUTIONS: Carcinogenicity).

Autoantibody formation

In controlled trials, the percentage of patients who developed new positive antinuclear antibodies (ANA) (≥1:40), new positive anti-double-stranded DNA antibodies and new anticardiolipin antibodies were increased compared to placebo-treated patients (11% cf. 5% respectively). The percentage of patients who developed new positive anti-double-stranded DNA antibodies was also higher by radioimmunoassay (15% of patients treated with ENBREL compared to 4% of placebo-treated patients) and by *Crithidia luciliae* assay (3% of patients treated with ENBREL compared to none of placebo-treated patients). The proportion of patients treated with ENBREL who developed anticardiolipin antibodies was similarly increased compared to placebo-treated patients.

Rare reports have been described in clinical trials and post-marketing experience, including patients with rheumatoid factor positive RA, who have developed additional antibodies in conjunction with autoimmune hepatitis, a lupus-like syndrome or rashes compatible with subacute cutaneous lupus or discoid lupus by clinical presentation and biopsy (see Other adverse reactions, below). The impact of long-term treatment with ENBREL on the development of autoimmune diseases is unknown. If a patient develops symptoms and findings suggestive of a lupus-like syndrome or autoimmune hepatitis following treatment with ENBREL, treatment should be discontinued and the patient should be carefully evaluated.

Psoriasis

Cases of new onset psoriasis, including pustular psoriasis and palmoplantar psoriasis, and cases of exacerbation of pre-existing psoriasis have been reported with the use of TNF blockers, including ENBREL. Many of these patients were taking concomitant immunosuppressants (e.g., MTX, corticosteroids). Some of these patients required hospitalisation. Most patients had improvements of their psoriasis following discontinuation of their TNF blocker. Some patients have had recurrences of the psoriasis when they were re-challenged with a different TNF blocker. Discontinuation of ENBREL should be considered for severe cases and those that do not improve or that worsen despite topical treatments.

Other adverse reactions

Events reported in at least 3% of all patients with higher incidence in patients treated with ENBREL compared to controls in placebo-controlled RA trials (including the combination methotrexate trial) and events per patient year are summarised in the next table.

Percent of Rheumatoid Arthritis Patients Reporting Adverse Events and Events per Patient Year in Placebo-Controlled Clinical Trials[a]

Event	Percent of Patients		Event per Patient Year	
	Placebo (n = 152)	ENBREL (n = 349)	Placebo (40 pt. years)	ENBREL (117 pt. years)
Injection site reaction	10	37	0.62	7.73
Infection	32	35	1.86	1.82
Non-upper respiratory infection [b]	32	38	1.54	1.50
Upper respiratory infection [b]	16	29	0.68	0.82
Headache	13	17	0.62	0.68
Rhinitis	8	12	0.35	0.45
Dizziness	5	7	0.25	0.21
Pharyngitis	5	7	0.17	0.24
Cough	3	6	0.17	0.18
Asthenia	3	5	0.10	0.16
Pain, Abdomen	3	5	0.12	0.17
Rash	3	5	0.12	0.21
Respiratory disorder	1	5	0.05	0.17
Dyspepsia	1	4	0.05	0.12
Sinusitis	2	3	0.07	0.12

a: Data from 3 trials including a 6-month study in which patients received concurrent methotrexate therapy.
b: Data from 2 of the 3 controlled trials.

Based on the results of clinical studies in rheumatoid arthritis, normally no special laboratory evaluations are necessary in addition to careful medical management and supervision of patients.

The following table of suspected adverse reactions is based on clinical trials and/or spontaneous post-marketing reports.

Adverse reaction frequencies are listed below in CIOMS frequency categories:

Very common: ≥ 10%

Common: ≥ 1% and < 10%

Uncommon: ≥ 0.1% and < 1%

Rare: ≥ 0.01% and < 0.1%

Very rare: < 0.01%

System	***Adverse Reaction***
Blood and Lymphatic System Disorders	
Uncommon	Thrombocytopenia
Rare	Anaemia, leucopenia, neutropenia, pancytopenia (see PRECAUTIONS)
Very Rare	Aplastic anaemia (see PRECAUTIONS)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Uncommon	Non-melanoma skin cancers

System	*Adverse Reaction*
Rare	Melanoma, lymphoma
Not known	Merkel cell carcinoma, leukaemia
Infections and Infestations	
Very Common	Infections (including upper respiratory tract infections, bronchitis, cystitis, skin infections)*
Common	Serious infections (including pneumonia, cellulitis, septic arthritis, sepsis, parasitic infection)*
Rare	Tuberculosis*, opportunistic infections (including invasive fungal, bacterial, protozoal and atypical mycobacterial infections, and *Legionella* infection)*
Not known	Listeriosis*, hepatitis B reactivation
Immune System Disorders	
Common	Allergic reactions; autoantibody formation
Uncommon	Systemic vasculitis (including ANCA positive vasculitis)
Rare	Serious allergic/anaphylactic reactions (including angioedema, bronchospasm), sarcoidosis
Not known	Macrophage activation syndrome
General Disorders and Administration Site Conditions	
Common	Fever
Respiratory, Thoracic and Mediastinal Disorders	
Uncommon	Interstitial lung disease (including pulmonary fibrosis and pneumonitis)
Nervous System Disorders	
Rare	Seizures, CNS demyelinating events including multiple sclerosis and localized demyelinating conditions such as optic neuritis and transverse myelitis
Very rare	Peripheral demyelinating events, including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy and multifocal motor neuropathy.
Eye Disorders	
Uncommon	Uveitis, ††scleritis
Skin and Subcutaneous Tissue Disorders	
Very Common	Injection site reactions
Common	Pruritus
Uncommon	Angioedema, rash, urticaria, psoriasis (new onset or exacerbation)** and psoriasiform rash
Rare	Cutaneous vasculitis (including leukocytoclastic vasculitis), Stevens-Johnson syndrome, erythema multiforme
Very rare	Toxic epidermal necrolysis
Musculoskeletal, Connective Tissue and Bone Disorders	
Rare	Subacute cutaneous lupus erythematosus, discoid lupus erythematosus, lupus-like syndrome
Cardiac Disorders	
Rare	Worsening of congestive heart failure
Hepatobiliary Disorders	

System	*Adverse Reaction*
Rare	Elevated liver enzymes, autoimmune hepatitis

*See additional information, under "Infections" above.

** See additional information under "Psoriasis" above.

Paediatric patients with juvenile idiopathic arthritis

In general, the adverse events in paediatric patients with juvenile idiopathic arthritis were similar in frequency and type to those seen in adult patients.

JIA patients treated with ENBREL had a significantly higher incidence of injection sites reactions (erythema and/or itching, pain or swelling) compared with placebo-treated patients in controlled clinical trials.

Infection was the most common adverse event reported in paediatric patients taking ENBREL and occurred at an incidence similar to placebo. The types of infections reported in JIA patients were generally mild and consistent with those commonly seen in outpatient paediatric populations.

In JIA clinical trials, two cases of varicella infection with signs and symptoms suggestive of aseptic meningitis have been reported among patients treated with ENBREL. There were also 4 reports of macrophage activation syndrome.

Long-term safety of ENBREL monotherapy (n=103), ENBREL plus methotrexate (n=294), or methotrexate monotherapy (n=197) were assessed for up to 3 years in a registry of 594 children aged 2 to 18 years with juvenile idiopathic arthritis, 39 of whom were 2 to 3 years of age. Overall, infections were more commonly reported in patients treated with ENBREL compared to methotrexate alone (3.8% versus 2%), and the infections associated with ENBREL use were of a more severe nature.

Paediatric patients with plaque psoriasis

In a 48-week study in 211 children aged 4 to 17 years with paediatric plaque psoriasis, the adverse events reported were similar to those seen in previous studies in adults with plaque psoriasis.

DOSAGE AND ADMINISTRATION

Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis or paediatric plaque psoriasis. Patients may self-inject only if their physician determines that it is appropriate and with medical follow-up, as necessary, after proper training in injection technique.

Adults

Rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis

The recommended dose of ENBREL is 50 mg per week, given as a subcutaneous injection, EITHER once weekly as a single 50 mg injection OR twice weekly as two separate 25 mg injections given 3-4 days apart.

Plaque psoriasis

The recommended dose of ENBREL is 50 mg per week, given once weekly (single 50 mg injection) or twice weekly (single 25 mg injections given 3-4 days apart) as a subcutaneous injection. Higher responses may be achieved from initial treatment for up to 12 weeks with a dose of 50 mg given twice weekly, after which, the dose should be reduced to the standard dose of 50 mg per week. If re-treatment with ENBREL is indicated, the dose used should be 50 mg per week.

Elderly patients

Elderly RA patients (age ≥ 65 years) show similar safety, efficacy and pharmacokinetic profiles compared to younger adult patients treated with ENBREL. Dose adjustment is not needed for the elderly. However, as with other medicinal products, greater sensitivity in some older patients cannot be ruled out.

Children and adolescents

The dosage of ENBREL is based on body weight for paediatric patients. Patients weighing less than 62.5 kg should be accurately dosed on a mg/kg basis using ENBREL powder for injection (see below for dosing for specific indications). Patients weighing 62.5 kg or more and receiving once weekly doses may be dosed using a 50 mg (in 1 mL) fixed-dose pre-filled syringe or auto-injector.

Juvenile idiopathic arthritis (age 2 years and above)

The recommended dose for children 2-17 years of age is 0.8 mg/kg (up to a maximum of 50 mg per dose) given once weekly as a subcutaneous injection, or 0.4 mg/kg (up to a maximum of 25 mg), given twice weekly with an interval of 3-4 days between doses.††

Paediatric plaque psoriasis (age 4 years and above)

The recommended dose is 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly for up to 24 weeks. Treatment should be discontinued in patients who do not show a significant PASI response after 12 weeks. If re-treatment with ENBREL is indicated, the above guidance on treatment duration should be followed.

Instructions for use, handling and disposal

Reconstitution (Powder for injection only)

ENBREL contains no antibacterial preservative and therefore, solutions prepared with water for injections should be administered as soon as possible and within six hours following reconstitution. In the absence of compatibility studies, ENBREL must not be mixed with other medicinal products.

Reconstitute the etanercept powder aseptically by injecting 1 mL of sterile water for injections very slowly into the vial with the vial adaptor attached to the syringe. Gently swirl the contents to avoid excessive foaming. Some foaming will occur, this is normal. To avoid excessive foaming, do not shake or vigorously agitate. Dissolution of ENBREL usually takes less than 10 minutes.

Visually inspect the solution for particulate matter and discolouration prior to administration. The solution should not be used if discoloured or cloudy, or if particulate matter remains. Withdraw the solution into the empty syringe, removing only the dose to be given from the vial. Some foam or bubbles may remain in the vial. Do not filter reconstituted solution during preparation or administration. Do not use ENBREL if all the powder in the vial is not dissolved within 10 minutes. Start again with another vial. Once the ENBREL solution has been aspirated into the syringe, discard the vial adaptor and replace with a needle from the pack for injection.

Before injecting

Sites for self-injection include thigh, abdomen or upper arm. Injection sites should be rotated. New injections should be given at least 3cm from an old site and never into areas where the skin is tender, bruised, red or hard (see Instruction sheet supplied with ENBREL).

Powder for injection: The reconstituted solution should be clear and colourless with no lumps, flakes or particles.

Pre-filled syringe (*Solution for injection)*: Before injecting, ENBREL single-use pre-filled syringes should be allowed to reach room temperature (approximately 15 to 30 minutes). The needle cover should not be removed during this period. The solution should be clear, colourless or pale yellow and practically free from visible particles. Otherwise, do not inject the solution. Use a different ENBREL pre-filled syringe, then contact your pharmacist for assistance.

Auto-injector (Solution for injection): Before injecting, ENBREL single-use Auto-injector should be allowed to reach room temperature (approximately 15 to 30 minutes). Immediate use is then recommended. The needle cover should not be removed while allowing the Auto-injector to reach room temperature. By looking though the inspection window, the solution should be clear and colourless or pale yellow and practically free from visible particles. Otherwise, do not inject the solution. Use a different ENBREL Auto-injector, then contact your pharmacist for assistance.

ENBREL is for single use only. Any unused product should be disposed of appropriately.

Administration

If a patient is to self-administer ENBREL, they should be instructed in injection techniques to ensure the safe self-administration of ENBREL (See Instruction sheet supplied with ENBREL). The first injection should be performed under the supervision of a qualified health care professional. The ability of that patient to self-inject subcutaneously should be assessed. A puncture-resistant container for disposal of needles and syringes should be used. Patients should be instructed in the technique and told the importance of proper syringe and needle disposal and be cautioned against reuse of these items.

Disposal

Contains no antimicrobial agent. Product is for single use only in one patient only. Discard any residue.

OVERDOSAGE

The maximum tolerated dose of ENBREL has not been established in humans. Repeat-dose studies have been performed in cynomolgus monkeys at doses resulting in AUC-based systemic exposure levels of etanercept that were over 13-fold higher than in humans at the highest proposed therapeutic dose of 50 mg and have revealed no dose-limiting or target organ toxicity. No dose-limiting toxicities were observed during clinical trials of RA patients. The highest dose level evaluated has been an IV loading dose of 32 mg/m^2 followed by SC doses of 16 mg/m^2 administered twice weekly. One RA patient mistakenly self-administered 62 mg ENBREL SC twice weekly for three weeks without experiencing unexpected side effects. Single IV doses up to 60 mg/m^2 (approximately twice the recommended dose) have been administered to healthy volunteers in an endotoxaemia study without evidence of dose-limiting toxicities.

There is no known antidote to ENBREL. For advice on the management of overdosage, please contact the Poisons Information Centre on 131 126.

PRESENTATION AND STORAGE CONDITIONS

Powder for injection

ENBREL powder for injection contains either 25 mg or 50 mg* of etanercept (rch). The content of the diluent is 1 mL of sterile water for injections.

ENBREL powder for injection cartons contain 4 clear glass vials (4 mL, Type 1 glass) with Teflon coated rubber stoppers, aluminium seals and flip-off plastic caps. ENBREL is also supplied with 4 pre-filled syringes containing 1 mL water for injections and 8 alcohol swabs. The pre-filled syringes are also made of Type 1 glass. Four vial adaptors and four 27 gauge needles are provided in the carton.

* not marketed

Pre-filled syringe (Solution for injection)

ENBREL solution for injection is supplied in a kit containing four single-dose pre-filled glass syringes containing ENBREL solution. Each syringe of ENBREL contains either 25 mg* (in 0.5 mL) or 50 mg (in 1 mL) of the active ingredient, etanercept (rch). The needle cover contains natural rubber (latex). Four alcohol swabs are also are provided in the carton.

* not marketed

Auto-injector (Solution for injection)

The ENBREL pre-filled Auto-injector contains 50 mg of etanercept (rch). The Auto-injector consists of a syringe made from clear Type 1 glass with a 27 gauge needle, rubber needle cover, and plastic plunger. The needle cap of the pre-filled Auto-injector contains dry natural rubber (a derivative of latex). Cartons contain 2*, 4 or 12* ENBREL Auto-injectors with 2, 4 or 12 alcohol swabs, respectively.

* not marketed

Storage

Powder for injection

Store at 2ºC to 8°C. Refrigerate. Do not freeze. The solution should be used immediately after reconstitution. If not used immediately, ENBREL solution must be refrigerated in the vial at 2°C to 8°C after reconstitution and used within 6 hours.

Prior to reconstitution, the powder may be stored at temperatures up to a maximum of 25°C for a single period of up to 4 weeks. ENBREL should be discarded if exposed to high temperatures, or if not used within 4 weeks of initial removal from refrigeration.

Solution for injection (Pre-filled syringe and Auto-injector)

Store at 2ºC to 8°C. Refrigerate. Do not freeze. May be stored at temperatures up to a maximum of 25°C for a single period of up to 4 weeks. ENBREL should be discarded if exposed to high temperatures, or if not used within 4 weeks of initial removal from refrigeration.

Keep the pre-filled syringes and the Auto-injectors in the outer carton in order to protect from light.

For additional advice on storing ENBREL, contact Pfizer Medical Information on 1800 675 229.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Limited
ABN: 50 008 422 348
38-42 Wharf Road
West Ryde NSW 2114

POISON SCHEDULE OF THE MEDICINE

S4, PRESCRIPTION ONLY MEDICINE

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

8 September 2000

DATE OF MOST RECENT AMENDMENT

12 February 2014

†† Please note changes to Product Information

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