Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Etanercept

Proprietary Product Name: Enbrel

Sponsor: Wyeth Australia Pty Ltd

May 2010

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Extension of Indications
Decision:	Approved
Date of Decision:	16 February 2010
Active ingredient(s):	Etanercept
Product Name(s):	Enbrel
Sponsor's Name and Address:	Wyeth Australia Pty Ltd Locked Bag 5002 Baulkham Hills BC NSW 2153
Dose form(s):	Powder for injection plus diluent Solution for injection in pre-filled syringe or Auto-injector.
Strength(s):	25 and 50 mg for powder for injection 50 mg for both solutions for injection
Container(s):	Powder for injection: 4 mL, type 1 glass vial with Teflon-coated rubber stopper, aluminium seal and flip-off plastic cap and a type 1 glass pre-filled syringe containing 1 mL Water for Injections Pre-filled syringe: single-dose pre-filled glass syringe with vial adaptor, 27 gauge needle and natural rubber needle cover Auto-injector: clear type 1 glass syringe with a 27 gauge needle, dry natural rubber needle cover and plastic plunger.
Pack size(s):	Powder for injection: 4 vials, 4 pre-filled syringes, 4 vial adaptors, 4 27 gauge needles and 8 alcohols swabs per carton. Solution for injection: 4 pre-filled syringes with 8 alcohol swabs per kit. Auto-injector: 4 Auto-injectors with 8 alcohol swabs per carton.
Approved Therapeutic use:	Treatment of adult patients with moderate to severe chronic plaque psoriasis, who are candidates for phototherapy or systemic therapy.
Route(s) of administration:	Subcutaneous
Dosage:	50 mg per week. In plaque psoriasis 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.

Product Background

Etanercept is a fusion protein combining the extracellular domain of the human tumour necrosis factor receptor-2 (TNFR2) with the Fc domain of human IgG1. It binds with tumour necrosis factor (TNF) and blocks its interaction with TNF receptors on cell surfaces and hence interrupts inflammatory pathways. It is currently approved for the treatment of psoriasis, after consideration by the Australian Drug Evaluation Committee (ADEC) at its February 2005 meeting. The current relevant approved indication is:

Treatment of adult patients with moderate to severe chronic plaque psoriasis, who are candidates for phototherapy or systemic therapy. Safety and efficacy beyond 12 months have not been demonstrated.

The current application seeks approval for the removal of the text "*Safety and efficacy beyond 12 months have not been demonstrated"* from the indication.

Etanercept is one of six biological agents approved for the systemic treatment of psoriasis in Australia in recent years (Table 1). The text "*Safety and efficacy beyond 12 months have not been demonstrated"*, or a similar statement to that effect, was included in the approved indication for the first four of these agents. The text was subsequently removed from the indication for alefacept, after the sponsor provided satisfactory long term data. The text was not included for adalimumab or ustekinumab, as long term (> 12 months) safety and efficacy data were available at the time of ADEC consideration for these two agents.

Etanercept is also approved for several rheumatology indications. None of these indications has a limiting statement regarding duration of treatment.

The other current approved indications are:

- Treatment of active adult rheumatoid arthritis (RA) in patients who have an inadequate response to one or more disease modifying antirheumatic drugs (DMARDs). Enbrel can be used in combination with methotrexate.
- Severe, active, adult rheumatoid arthritis to slow progression of disease-associated structural damage in patients at high risk of erosive disease.
- Active polyarticular-course juvenile idiopathic arthritis in patients (4 to 17 years) who have had inadequate response to one or more disease-modifying anti-rheumatic drugs. Enbrel has not been studied in children less than 4 years of age.
- The treatment of 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).
- The treatment of the signs and symptoms of active ankylosing spondylitis in adults.

Regulatory Status

A similar application to the current Australian submission has been approved in the US (30 September 2009, the European Union (EU) (16 July 2009) and Canada (11 August 2008).

In the US, based on studies 115 and 117, the sentence *Efficacy and safety of Enbrel treatment beyond 12 months has not been adequately evaluated in patients with psoriasis* was deleted from the Clinical Trials section of the US product information (PI).

In the EU, based on studies 115 and 117, a sentence was added to section 5.1 Pharmacodynamic effects/Clinical Trials of the Summary of Product Characteristics:

In long term (up to 34 months) open-label studies where Enbrel was given without interruption, clinical responses were sustained and safety was comparable to shorter-term studies.

In Canada, the long term data for adult psoriasis (96 week) was submitted in a Supplemental New Drug Submission (SNDS). The "12 month" statement in relation to psoriasis was never present in the Canadian PI.

Table 1: Registered biological agents for psoriasis

Generic name (tradename)	Sponsor	Approval Year	Mechanism of Action	Registered indication
Alefacept (Amevive)	Biogen Idec	2004	LFA-3/CD2 interaction inhibition	Treatment of adult patients with moderate to severe chronic plaque psoriasis, who are candidates for phototherapy or systemic therapy. Safety and efficacy beyond 2 courses have not been demonstrated. (1)
Efalizumab (Raptiva)	Serono	2004	LFA-1/ICAM-1 interaction inhibition	Treatment of adult patients with moderate to severe chronic plaque psoriasis, who are candidates for phototherapy or systemic therapy. Safety and efficacy beyond 12 months have not been established.
Etanercept (Enbrel)	Wyeth	2005	TNF alpha inhibition	Treatment of adult patients with moderate to severe chronic plaque psoriasis, who are candidates for phototherapy or systemic therapy. Safety and efficacy beyond 12 months have not been demonstrated.
Infliximab (Remicade)	Schering-Plough	2006	TNF alpha inhibition	Treatment of adult patients with moderate to severe plaque psoriasis for whom phototherapy or conventional systemic treatments have been inadequate or are inappropriate. Safety and efficacy beyond 12 months have not been established.
Adalimumab (Humira)	Abbott	2008	TNF alpha inhibition	Treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.
Ustekinumab (Stelara)	Janssen-Cilag	2009	IL-12 and IL-23 receptor blockade	Treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

Notes: (1) Initial TGA approval included the statement that 'Safety and efficacy beyond 2 courses have not been demonstrated.' This restriction was removed after provision of long term data.

Product Information

The approved product information current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Quality Summary and Conclusions

There is no requirement for a quality evaluation in an application of this type.

III. Nonclinical Findings

Nonclinical Summary and Conclusions

There is no requirement for a nonclinical evaluation in an application of this type.

IV. Clinical Findings

Introduction

The sponsor submitted a Phase III, double-blind, placebo-controlled, randomized, multicentre study (Study 20030117) in subjects with psoriasis and a Phase III, open, long-term, extension study (Study 20030115) of etanercept in the treatment of psoriasis in adult patients.

The objectives of these two studies were to determine the efficacy, safety and tolerability of either once weekly (QW) or twice weekly (BIW) dosing regimens of etanercept 50 mg in subjects with psoriasis over a period up to 96 weeks and to characterize the pharmacokinetic profile of etanercept 50 mg BIW up to week 96.

Pharmacokinetics

Study 20030117: The key issue addressed in this study was that etanercept levels in the placebo/etanercept arm were comparable to that in the etanercept/ etanercept arm after the initiation of etanercept at Week 12 in the placebo arm. Samples were obtained from all subjects at baseline and at pre-dose at Weeks 12, 24, 36, 48, 60, 72, 84, and 96 to determine etanercept plasma concentrations.

Study 20030115: The key issue addressed in this study was the feasibility of dose change to 50 mg QW from 25 mg BIW in the parent study. Serum samples from a subset of 84 subjects from selected sites were obtained and measured. The results demonstrated that the etanercept weekly exposure at steady state is similar with both the 50 mg QW and 25 mg BIW doses. These data were previously evaluated by the TGA.

Pharmacodynamics

No new data were submitted.

Efficacy

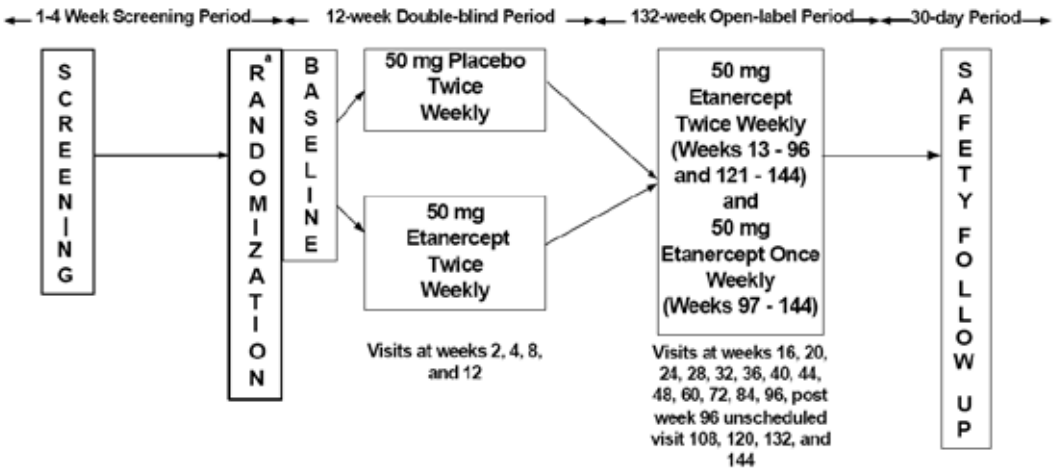
Study 20030117, an ongoing phase III study was conducted as a double-blind, randomized, placebo-controlled study over 12 weeks, in subjects with psoriasis, followed by an open label treatment period lasting 132 weeks. The primary analysis was done at 12 weeks. No interim analyses were planned, but since the study was extended to 144 weeks, an additional summary of the Week 96 data was provided.

The subjects were stratified at randomisation into those previously exposed to systemic therapy/phototherapy and those who were treatment naïve.

Systemic therapy included: cyclosporin; systemically administered calcineurin inhibitors (for example, intravenous or oral tacrolimus); methotrexate; azathioprine; cyclophosphamide; thioguanine; oral retinoids; hydroxyurea; fumarates; systemic steroids; phototherapy (either psoralen ultraviolet A [PUVA] or ultraviolet B [UVB]); or any parenterally administered biologic response modifier given for psoriasis, including but not limited to alefacept, siplizumab, efalizumab, anti-IL-8mAb, and anti-CD2 mAb.

The subjects, after randomisation, received either placebo or etanercept 50 mg BIW subcutaneously (SC) for the initial 12 week period. This was followed by an open label period during which all the patients received etanercept 50 mg BIW SC up to Week 96. At the Week 96 visit, the dose was reduced to 50 mg QW for the next 24 weeks. Those who did not maintain clinical efficacy had dose escalation to 50 mg BIW at the Week 120 or Week 132 visit till study close at Week 144. See Figure 1, below:

Figure 1 Schema for study 20030117



[a] Subjects were considered enrolled after they had been determined eligible for the study and the randomization call was made to t andomization could occur up to 3 days before the first dose of investigational product on day 1. Baseline was performed on day 1. The allocation ratio was 1:1 etanercept to placebo.

Study 20030115 was a Phase III open-label, long-term study of etanercept in subjects who had participated in one of two etanercept psoriasis studies (1639 and 1642). These two studies were previously evaluated by TGA. In this study, all the subjects were treated with etanercept 50 mg QW SC for 12 weeks. At Week 12, those who failed to achieve PASI 75 or had significant residual disease despite achieving PASI 75, had their dose escalated to 50 mg BIW. [1] The treatment duration was a minimum of 48 weeks and a maximum of 72 weeks. Interpretation of efficacy results beyond 48 weeks was limited because the study was deemed to have closed when the last subject reached the Week 48 visit. Subjects were considered "dose interrupted" if > 30 days had elapsed between the last dose in the parent study and the first dose in this study. These subjects had additional eligibility criteria that were required to be met, before inclusion in this study.

The patient population in both studies were subjects > 18 years, with active but clinically stable plaque psoriasis involving > 10% of the body surface area, had a minimum PASI of 10 at screening, had received at least 1 previous phototherapy or systemic psoriasis therapy or were a candidate to receive phototherapy or systemic psoriasis therapy.

[1] Psoriasis Area and Severity Index (PASI): Total PASI scores were calculated by multiplying the area of involvement score, the sum of the severity scores for erythema, induration, and scaling, and a weight factor for that body area (0.1, 0.2, 0.3, and 0.4 for head, upper extremities, trunk, and lower extremities, respectively), and then summing across all 4 body areas. The total range of the PASI score is 0 to 72, where 0 = no psoriasis and 72 = severe disease. PASI 75 represents a 75% improvement in the PASI score.

Statistical methods

In **study 20030117**, the planned sample size of 600 subjects was chosen, based on results from previous studies, to provide adequate exposure to etanercept 50 mg BIW for evaluation of safety endpoints.

In **study 20030115**, the sample size was dependent on the number who participated in the parent studies (1639 and 1642) and elected to continue treatment in this study.

In **study 20030117** the primary efficacy end-point was the PASI 75 response (at least a 75% improvement in the PASI score from baseline) at Week 12, in subjects with psoriasis treated with etanercept 50 mg BIW or placebo.

In **study 20030115**, efficacy was a secondary endpoint in subjects with psoriasis treated with etanercept 50 mg QW/BIW, and assessed by PASI 50, 75 and 90 at 12, 24 and 48 weeks.

The secondary efficacy endpoints included:

- PASI 50, 75 and 90 at other time points.
- Physician's static global assessment of psoriasis (sPGA) at scheduled visits.[2]
- Dermatology Life Quality Index (DLQI) response (defined as at least a 5 point improvement from baseline or a 0-score in DLQI at Week 12).[3]
- Response in Hamilton depression scale and Beck depression inventory.[4,5]
- Improvement from baseline in FACIT fatigue scale.[6]
- Subject assessment of itching, improvement in joint pain and psoriasis pain VAS (visual analogue scale).[7]

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[2] Physician's static Global Assessment (sPGA): Physician-reported measure of psoriasis progression was the static physician's global assessment of psoriasis which was scored on a scale of 0 to 5, where 0 = clear disease and 5 = severe disease.

[3] Dermatology Life Quality Index (DLQI): The DLQI is a validated subject-reported outcome questionnaire that consists of 10 items that assess how much a skin problem has affected the subject over the past week. The DLQI score is calculated as an equal-weighted summary of the items (range 0 to 30), and higher scores indicate poorer outcomes. This score is composed of 6 subscales that measure symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment.

[4] The Hamilton Rating Scale for Depression (HAM-D): This is a questionnaire administered to the subjects by trained health care professionals. The Ham-D score (range 0 to 53) is calculated from an equal-weight summary of 17 items, and higher total scores indicate more severe depression. Each question is rated from 0 to 2, 3, or 4 for severity.

[5] Beck Depression Index (BDI): This is a subject-administered questionnaire. The BDI score (range 0 to 63) is calculated from an equal-weight summary of 21 symptoms and attitudes, each of which is rated from 0 to 3 for severity, and higher total scores indicate more severe depression.

[6] Functional Assessment of Chronic Illness Therapy (FACIT): The FACIT fatigue score has a range of 0 to 52, and in this case a higher total score is better. The questionnaire includes 13 questions regarding how fatigue affected the subject's activities over the previous 7 days. Each question is answered on a scale of 0 to 4, where 0 = not at all and 4 = very much.

- Improvement in nail psoriasis index (NAPSI) score.[8]

There were two study amendments for each of the studies. The changes were mainly related to statistical methods and were unlikely to change the study outcomes.

In **study 20030115,** the amendment allowed a PK study of the 50 mg QW exposure in this study.

Results

Study population

In **study 20030117**, a total of 618 subjects received at least one dose of study treatment. The most common reason for discontinuation was withdrawal of consent, closely followed by adverse events (Table 4). About a third of the subject population was female and about 90% were white. The mean age was 46 years. The mean duration of psoriasis was 20 years and the mean affected body surface area was 27%. The stratification performed at randomisation was balanced between the placebo and etanercept treatment arms. A total of 75% of the subjects had received prior psoriasis therapy.

Table 4: Reason for investigational product discontinuation during open-label period through Week 96 in Study 20030117

[7] Subject assessments of psoriasis and itching: These were reported on a 6-point scale where 0 = good ("none" for itching) and 5 = severe. Subject assessments of skin pain and joint pain were reported on a VAS of 0 to 10, where 0 = no pain and 10 = severe pain.

[8] The Nail Psoriasis Severity Index (NAPSI): Nails (excluding thumbnails) were graded by dividing the nail with imaginary horizontal and vertical lines into 4 quarters, and then scoring each quarter for presence (1) or absence (0) of pitting, leukonchya, red spots in lunula, nail plate crumbling, oil drop (salmon patch) discoloration, onycholysis, nail bed hyperkeratosis, and splinter haemorrhages (possible score of 0 – 32 per nail). Only subjects whose worst nail at baseline had a minimum score of 6 on the 0 to 32 NAPSI scale were followed for NAPSI assessment during the study.

	Placebo / Etanercept 50 mg BIW (N=287)	Etanercept 50 mg BIW / Etanercept 50 mg BIW (N=304)	All (N=591)
Withdrew From Investigational Product During OL Through Wk 96			
No	231 (80.5)	233 (76.6)	464 (78.5)
Yes	56 (19.5)	71 (23.4)	127 (21.5)
Subject Status			
Completed 96 Weeks of Investigational Product	231 (80.5)	233 (76.6)	464 (78.5)
Protocol deviation	0 (0.0)	1 (0.3)	1 (0.2)
Noncompliance	5 (1.7)	7 (2.3)	12 (2.0)
Adverse event	15 (5.2)	16 (5.3)	31 (5.2)
Consent withdrawn	17 (5.9)	29 (9.5)	46 (7.8)
Disease progression	5 (1.7)	9 (3.0)	14 (2.4)
Administrative decision	1 (0.3)	0 (0.0)	1 (0.2)
Lost to follow-up	9 (3.1)	7 (2.3)	16 (2.7)
Death	2 (0.7)	0 (0.0)	2 (0.3)
Pregnancy	1 (0.3)	1 (0.3)	2 (0.3)
Other	1 (0.3)	1 (0.3)	2 (0.3)

N = Number of subjects who received at least 1 dose of open-label investigational product

In **study 20030115**, a total of 912 subjects received at least one dose of etanercept. A total of 591 subjects (64.8%) eventually dose escalated to 50 mg BIW after 12 weeks. The other 321 subjects (35.2%) remained on the 50 mg QW dose. A total of 818 subjects (89.7%) completed 48 weeks and 485 subjects (53.2%), 72 weeks of treatment. The most common reason for withdrawal from the study was “lost to follow-up”, followed by withdrawal of consent and adverse events (Table 5). The demographics of the subject population and their disease characteristics were similar to that in study 20030117 except that the mean PASI score had improved from the parent study baseline mean of 18.9 to the present study baseline of 7.95 and the incidence of psoriatic arthritis was lower than in study 20030117 (25% vs 34%).

Table 5: Subject disposition in Study 20030115

	Etanercept 50 mg QW		Etanercept 50 mg QW / 50 mg BIW		
	20021639 (N=155)	20021642 (N=166)	20021639 (N=284)	20021642 (N=307)	All (N=912)
Subject Status - n(%) (Study Status)					
Completed Study	113 (72.9)	143 (86.1)	267 (94.0)	299 (97.4)	822 (90.1)
Ineligibility determined	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Protocol deviation	1 (0.6)	2 (1.2)	0 (0.0)	0 (0.0)	3 (0.3)
Noncompliance	1 (0.6)	1 (0.6)	0 (0.0)	0 (0.0)	2 (0.2)
Adverse Event	12 (7.7)	3 (1.8)	3 (1.1)	1 (0.3)	19 (2.1)
Consent Withdrawn	7 (4.5)	4 (2.4)	6 (2.1)	3 (1.0)	20 (2.2)
Disease progression	4 (2.6)	3 (1.8)	3 (1.1)	2 (0.7)	12 (1.3)
Administrative decision	2 (1.3)	1 (0.6)	0 (0.0)	0 (0.0)	3 (0.3)
Lost to follow-up	10 (6.5)	8 (4.8)	4 (1.4)	1 (0.3)	23 (2.5)
Pregnancy	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.3)	2 (0.2)
Other	4 (2.6)	0 (0.0)	1 (0.4)	0 (0.0)	5 (0.5)
Test Article Status - n(%) (Treatment Status)					
Unknown[a]	17 (11.0)	35 (21.1)	32 (11.3)	32 (10.4)	116 (12.7)
Completed test article administration	95 (61.3)	103 (62.0)	225 (79.2)	260 (84.7)	683 (74.9)
Ineligibility determined	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Protocol deviation	1 (0.6)	2 (1.2)	0 (0.0)	0 (0.0)	3 (0.3)
Noncompliance	1 (0.6)	1 (0.6)	1 (0.4)	1 (0.3)	4 (0.4)
Adverse event	13 (8.4)	4 (2.4)	4 (1.4)	2 (0.7)	23 (2.5)
Consent withdrawn	7 (4.5)	5 (3.0)	10 (3.5)	5 (1.6)	27 (3.0)
Disease progression	4 (2.6)	3 (1.8)	3 (1.1)	3 (1.0)	13 (1.4)
Administrative decision	2 (1.3)	1 (0.6)	0 (0.0)	0 (0.0)	3 (0.3)
Lost to follow-up	10 (6.5)	9 (5.4)	7 (2.5)	2 (0.7)	28 (3.1)
Pregnancy	0 (0.0)	2 (1.2)	0 (0.0)	2 (0.7)	4 (0.4)
Other	4 (2.6)	1 (0.6)	2 (0.7)	0 (0.0)	7 (0.8)

[a] Reason for treatment ending was not stated on CRF

N=Number of subjects who received at least 1 dose of investigational product.

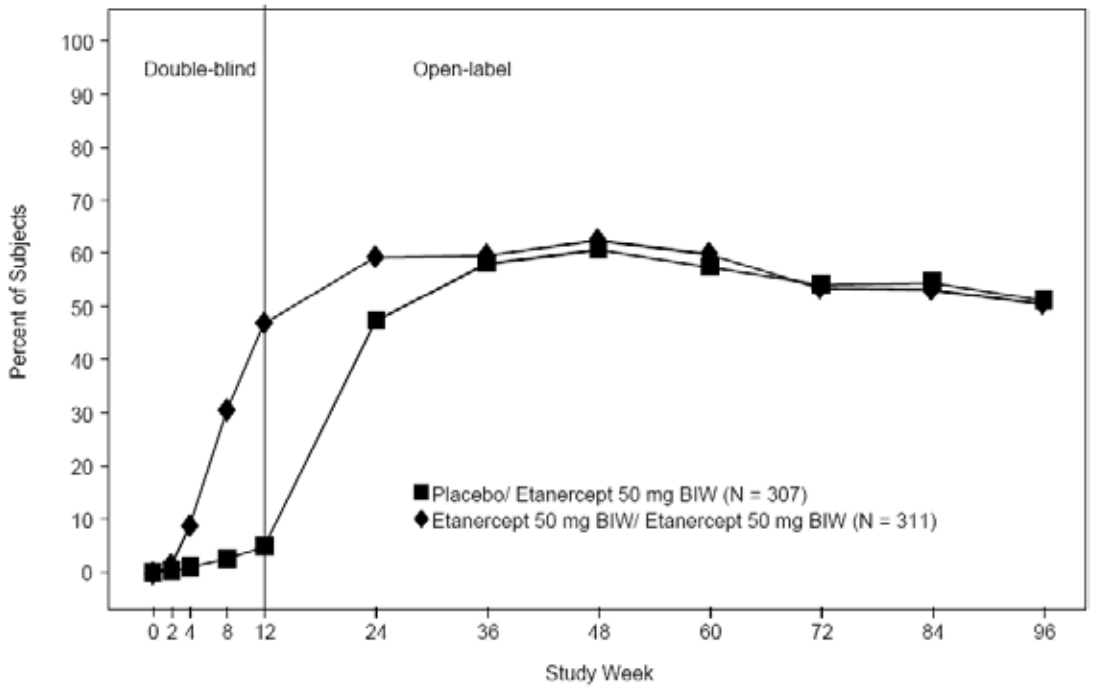
Efficacy results

PASI response

In **study 20030117**, the PASI 75 response in the etanercept arm was 47% compared with 5% in the placebo arm at the Week 12 visit. Following initiation of etanercept therapy in the placebo arm in the open label phase of the study, the placebo group showed the same progress made by the etanercept group in the first 12 weeks of the study. Efficacy as measured by PASI response declined (5% to 20%) between 48 weeks and 96 weeks of treatment (Figure 2). While the decline in PASI 50 response was smaller (5-10%), the PASI 75 and PASI 90 responses declined by about 20%. This decline was considered to be partly due to subject non-compliance with etanercept therapy. In an analysis of the effect of compliance on the results, it was found that subjects who were less than 90% compliant

between weeks 48 and 96 showed a PASI 75 decline of > 20% while subjects with > 90% compliance had a PASI 75 decline of about 10%. The PASI score over time reflects this.

Figure 2: Percent of subjects achieving PASI 75 response over time (LOCF) in Study 20030117



N = Number of subjects who were randomized and received at least 1 dose of investigational product

In **study 20030115**, the PASI 50, 75 and 90 scores at Week 48 were similar to the respective scores at Week 72 for non-dose escalators and dose escalators (Table 6). The rate of PASI 50, 75 and 90 responses were largely unchanged from Week 48 to Week 72. This result was reflected in the analysis of PASI score over time in the dose escalated and non escalated groups (Table 7). The duration of dose interruption between the parent study and this study had no bearing on PASI responses between Week 48 and Week 72.

Table 6: Mean (SE) PASI score (LOCF) from parent study baseline in Study 20030115

Open-label Etanercept	Without Dose Escalation 50 mg QW		With Dose Escalation 50 mg QW/BIW	
	n		n	
Baseline[a]	319	6.3 (0.4)	588	8.9 (0.3)
Week 12	305	4.3 (0.3)	588	7.4 (0.3)
Week 24	308	4.1 (0.3)	588	8.0 (0.2)
Week 36	308	3.9 (0.3)	588	7.1 (0.2)
Week 48	308	3.9 (0.3)	588	6.0 (0.2)
Week 60	308	4.1 (0.3)	588	5.7 (0.2)
Week 72	308	4.2 (0.3)	588	6.1 (0.2)

[a] Baseline of Study 20030115

Table 7: Mean (SE) PASI score percent improvement from parent study baseline (LOCF) in Study 20030115

Open-label Etanercept	Without Dose Escalation 50 mg QW		With Dose Escalation 50 mg QW/BIW	
	n	Mean (SE)	n	
Baseline[a]	319	64.8 (1.6)	588	53.5 (1.3)
Week 12	305	75.4 (1.2)	588	60.4 (1.1)
Week 24	308	76.4 (1.2)	588	57.0 (1.1)
Week 36	308	77.4 (1.3)	588	61.7 (1.0)
Week 48	308	77.4 (1.3)	588	67.3 (0.9)
Week 60	308	76.2 (1.3)	588	69.3 (0.8)
Week 72	308	75.8 (1.3)	588	67.1 (0.9)

[a] Baseline of Study 20030115

sPGA

The Physician's Static Global Assessment of psoriasis was scored on a scale from 0 (clear disease with no evidence of plaque elevation, erythema, or scale) to 5 (severe induration, erythema and scaling). In **study 20030117**, clear status (0) was achieved by 9% in the

etanercept/placebo arm and 12% in the etanercept/etanercept arm. The results were largely unchanged at week 96 with about 9% in both arms being clear. The percentage achieving a clear/almost clear status declined from 52% and 48% to 39% and 41% respectively in the placebo/etanercept and etanercept/etanercept arms (Table 8).

Table 8: Physicians Static Global Assessment of Psoriasis Over Time - Clear and Clear/Almost Clear status (LOCF) in Study 20030117

		Placebo/ Etanercept 50 mg BIW	Etanercept 50 mg BIW/ Etanercept 50 mg BIW	p-value[a]
Clear (0)	Baseline	0/307 (0%)	0/311 (0%)	N/A
	Week 1	0/283 (0%)	0/283 (0%)	N/A
	Week 2	0/305 (0%)	0/309 (0%)	N/A
	Week 4	0/306 (0%)	1/311 (<1%)	0.3225
	Week 8	1/306 (<1%)	7/311 (2%)	0.0351
	Week 12	1/306 (<1%)	21/311 (7%)	<0.0001
	Week 24	19/306 (6%)	33/311 (11%)	
	Week 36	31/306 (10%)	41/311 (13%)	
	Week 48	28/306 (9%)	38/311 (12%)	
	Week 60	30/306 (10%)	36/311 (12%)	
	Week 72	33/306 (11%)	31/311 (10%)	
	Week 84	32/306 (10%)	28/311 (9%)	
	Week 96	26/306 (8%)	28/311 (9%)	
Clear/Almost Clear (0,1)	Baseline	0/307 (0%)	0/311 (0%)	N/A
	Week 1	1/283 (<1%)	1/283 (<1%)	0.9974
	Week 2	4/305 (1%)	13/309 (4%)	0.0289
	Week 4	6/306 (2%)	40/311 (13%)	<0.0001
	Week 8	15/306 (5%)	114/311 (37%)	<0.0001
	Week 12	18/306 (6%)	151/311 (49%)	<0.0001
	Week 24	152/306 (50%)	159/311 (51%)	
	Week 36	161/306 (53%)	154/311 (50%)	
	Week 48	160/306 (52%)	148/311 (48%)	
	Week 60	153/306 (50%)	137/311 (44%)	
	Week 72	134/306 (44%)	132/311 (42%)	
	Week 84	131/306 (43%)	128/311 (41%)	
	Week 96	120/306 (39%)	126/311 (41%)	

[a] Two-sided Cochran-Mantel-Haenszel test stratified by prior psoriasis therapy

In **study 20030115**, a clear status (0) was achieved by 12% at Weeks 48 and 72 by the non dose escalators and only 2% at each time-point by the dose escalators. A clear/almost clear status (0/1) was achieved by 54% of the non dose escalators and 28% of the dose escalators at 48 weeks. This disparity in outcomes was seen through to 72 weeks (Table 9).

Table 9: Static Physician's Global Assessment of Psoriasis - - Clear and Clear/Almost Clear status (LOCF) in Study 20030115

Open-label Etanercept		Without Dose Escalation 50 mg QW	With Dose Escalation 50 mg QW/BIW
Clear (0)	Baseline[a]	15/319 (5%)	10/588 (2%)
	Week 12	33/305 (11%)	6/588 (1%)
	Week 24	29/308 (9%)	6/588 (1%)
	Week 36	40/308 (13%)	3/588 (1%)
	Week 48	36/308 (12%)	11/588 (2%)
	Week 60	32/308 (10%)	9/588 (2%)
	Week 72	37/308 (12%)	11/588 (2%)
Clear/Almost Clear (0,1)	Baseline[a]	116/319 (36%)	145/588 (25%)
	Week 12	167/305 (55%)	155/588 (26%)
	Week 24	170/308 (55%)	106/588 (18%)
	Week 36	171/308 (56%)	126/588 (21%)
	Week 48	167/308 (54%)	166/588 (28%)
	Week 60	168/308 (55%)	172/588 (29%)
	Week 72	157/308 (51%)	157/588 (27%)

[a] Baseline of 20030115

DLQI

The scores range from 0 to 30 with higher scores indicating poorer outcomes.

In **study 20030117**, there was some improvement with time, with the scores declining from Week 48 to Week 96 in both arms of the study. The decline was fairly small (73.1 to 68.3 and 74.6 to 67.3 in the etanercept/placebo and the etanercept/etanercept arms respectively). The mean score in each of the 6 DLQI subscales (symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment) showed the same pattern. The proportion of subjects that achieved a 0 score was similar at Weeks 48 and 96 (Table 10).

Table 10: DLQI score over time (LOCF) in Study 20030117

		Placebo / Etanercept 50 mg BIW	Etanercept 50 mg BIW / Etanercept 50 mg BIW	p-value[a]
0 Score	Baseline	1/304 (<1%)	1/308 (<1%)	0.9951
	Week 1	4/282 (1%)	1/283 (<1%)	0.1769
	Week 2	6/305 (2%)	8/309 (3%)	0.6064
	Week 4	10/306 (3%)	18/311 (6%)	0.1303
	Week 8	10/306 (3%)	56/311 (18%)	<0.0001
	Week 12	10/306 (3%)	86/311 (28%)	<0.0001
	Week 24	86/306 (28%)	110/311 (35%)	
	Week 36	104/306 (34%)	113/311 (36%)	
	Week 48	109/306 (36%)	114/311 (37%)	
	Week 60	110/306 (36%)	102/311 (33%)	
	Week 72	105/306 (34%)	93/311 (30%)	
	Week 84	108/306 (35%)	84/311 (27%)	
	Week 96	101/306 (33%)	86/311 (28%)	

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[a] Two-sided Cochran-Mantel-Haenszel test stratified by prior psoriasis therapy

In **study 20030115**, the non dose escalators showed greater improvement than the dose escalators. The scores, in both arms, improved after Week 12 and were maintained to Week 72. The results for the 6 DLQI subscales were similar.

A '0' score was achieved by 34% of the non dose escalators at Week 12 and the result was maintained at Week 72. A '0' score was achieved by 13% of dose escalators at Week 12 and 20% at Week 72 (Table 11).

Table 11: DLQI – 0 score (LOCF) in Study 20030115

Open-label Etanercept		Without Dose Escalation 50 mg QW	With Dose Escalation 50 mg QW/BIW
0 Score	Baseline[a]	76/315 (24%)	56/581 (10%)
	Week 12	103/305 (34%)	75/588 (13%)
	Week 24	100/308 (32%)	56/588 (10%)
	Week 36	101/308 (33%)	85/588 (14%)
	Week 48	104/308 (34%)	112/588 (19%)
	Week 60	105/308 (34%)	110/588 (19%)
	Week 72	102/308 (33%)	115/588 (20%)

[a] Baseline of 20030115

Depression

Depression was measured in **study 20030117** using the health-care professional administered questionnaire (HAM-D) or the self administered questionnaire (BDI).

The HAM-D results showed that the majority of subjects in the placebo/etanercept and the etanercept/etanercept arms had no symptoms of depression at 48 weeks (88% and 87% respectively). The improvement achieved at Week 48 was maintained through to Week 96.

BDI has a score range of 0-63, with higher scores indicating more severe depression. As with the HAM-D scoring system, the improvement in the symptoms of depression was similar in the two arms of the study at Week 48 and was maintained to Week 96.

The FACIT fatigue scale

In **study 20030117**, the FACIT fatigue scale showed improvement in the etanercept/etanercept arm and the placebo/etanercept arm after initiation of etanercept therapy. The improvement was maintained and showed the highest level of improvement at Week 96.

Antibodies and the relationship to efficacy

In **study 20030117**, the presence of non-neutralizing anti-etanercept antibodies did not have any effect on the efficacy profile of etanercept. This result was supported by the results from **study 20030115.** Neutralizing anti-etanercept antibodies were not detected in any of the subjects of study 20030117 or 20030115.

Efficacy conclusions

The gains in efficacy that was achieved in the first 48 weeks remained largely unchanged from Week 48 to Week 96 in study 20030117 and from Week 48 to Week 72 in study 20030115.

In study 20030117, efficacy as measured by PASI response declined between 48 weeks and 96 weeks of treatment. While the decline in PASI 50 response was small (5-10%), the PASI 75 and PASI 90 responses declined by about 20%. This decline was considered to be partly due to subject non-compliance with etanercept therapy. The analysis of the impact of compliance on PASI response supported this belief.

In study 20030115, the PASI 75 response at 48 weeks among the non dose escalators was similar to that in study 20030117 with two thirds achieving a PASI 75 response. The PASI 50 scores at 48 and 72 weeks remained unchanged. The PASI 75 and PASI 90 responses at Weeks 48 and 72, were similar.

In study 20030117, the results of sPGA showed a little decline in results from week 48 to week 96. The percentage achieving a clear status remained the same but those achieving a clear/almost clear status declined from 52% and 48% to 39% and 41% respectively in the placebo/etanercept and etanercept/etanercept arms. In study 20030115, the results of sPGA remained unchanged from Week 48 through to Week 72.

Etanercept therapy had a beneficial effect on the symptoms of depression and fatigue as measured by the HAM-D scale, the BDI scoring system and the FACIT fatigue scale. The results remained unchanged from Week 48 through to Week 96.

Safety

The safety data was obtained from the two studies (**20030117 and 20030115**).

In **study 20030117**, the 'placebo subjects' were those who received at least 1 dose of placebo during the first 12 weeks of the study (total = 306). The 'etanercept subjects' were those who received at least 1 dose of etanercept (total = 598). The mean exposure to etanercept for all subjects in the open label period through Week 96 was 517.58 days with similar exposure in the two arms of the study (Table 12).

Table 12: Investigational product administered during open-label period through Week 96 in Study 20030117

	Placebo / Etanercept 50 mg BIW (N=287)	Etanercept 50 mg BIW / Etanercept 50 mg BIW (N=304)	All (N=591)
Number of Doses			
n	287	304	591
Mean	145.57	143.97	144.75
SD	41.84	42.34	42.07
Median	165.00	164.00	164.00
Min, Max	2.0, 168.0	1.0, 168.0	1.0, 168.0
Duration of Dosing (Days)			
n	287	304	591
Mean	521.10	514.25	517.58
SD	147.06	150.33	148.66
Median	585.00	585.00	585.00
Min, Max	4.0, 596.0	1.0, 596.0	1.0, 596.0

N = Number of subjects who received at least 1 dose of open-label investigational product

Exposure-adjusted event (EAE) rates per 100 subject years were calculated by the following formula:

100 * (number of adverse events) / (total number of exposure years to the study product)

The EAE rates for adverse events through the double-blind and open label periods up to Week 96 was higher for subjects while on placebo than while on etanercept. However, it must be remembered that the number of exposure years while on placebo is > 10 fold lower (Table 13).

Table 13: Summary of Adverse Event Exposure-adjusted Rates through Week 96 in Study 20030117

Types of Events	Placebo (N = 306) (E = 65.9) n	r	Etanercept 50 mg BIW (N = 598) (E = 908.9) n	r
All Events	366	(555.3)	2491	(274.1)
All Non-infectious Adverse Events	276	(418.8)	1436	(158.0)
All Infections	86	(130.5)	944	(103.9)
Serious Non-infectious Adverse Events	4	(6.1)	70	(7.7)
Death	0	(0.0)	2	(0.2)
Serious Infections	1	(1.5)	11	(1.2)
Grade 3 Non-infectious Adverse Events	12	(18.2)	69	(7.6)
Grade 3 Infections	2	(3.0)	21	(2.3)
Non-infectious Adverse Events Leading to Withdrawal From Study	6	(9.1)	29	(3.2)
Infections Leading to Withdrawal From Study	1	(1.5)	6	(0.7)
All Injection Site Reactions	4	(6.1)	111	(12.2)

N = Number of subjects who were randomized and received at least 1 dose of investigational product
E = Total number of exposure years
n = Number of adverse events
r = Exposure-adjusted event rate per 100 subject years (= n / E * 100)

In **study 20030115**, there were 321 non dose escalators and 591 dose escalators. The mean exposure to etanercept for all the subjects who had at least one dose of etanercept was 421.58 days (Table 14). The EAE rate for dose escalators and non dose escalators were comparable (Table 15).

Table 14: Extent of exposure in Study 20030115

		Subject With Dose Escalation				
	Subjects Without Dose Escalation Etanercept 50 mg QW (N=321)	Etanercept 50 mg QW / 50 mg BIW (N=591)	Etanercept 50 mg QW Exposure (N=591)	Etanercept 50 mg BIW Exposure (N=591)	All Subjects Etanercept 50 mg QW Exposure (N=912)	All Etanercept (N=912)
Duration of Dosing (Days)						
n	321	591	591	591	912	912
Mean	372.57	448.20	213.69	234.51	269.61	421.58
SD	148.41	70.86	57.64	74.01	125.11	110.88
Median	414.00	498.00	200.00	246.00	230.00	495.00
Min	1.0	198.0	80.0	1.0	1.0	1.0
Max	512.0	509.0	477.0	421.0	512.0	512.0

N=Number of subjects who received at least 1 dose of investigational product.

Table 15: Summary of Exposure-adjusted Adverse Event rates through end of the study - All subjects by dose escalating status in Study 20030115.

	Etanercept					
	50 mg QW Only (N = 321) (E = 327.4)		50 mg QW / 50 mg BIW (N = 591) (E = 728.8)		All (N = 912) (E = 1056.2)	
Types of Adverse Events	n	r	n	r	n	r
All Events	834	(254.7)	1656	(227.2)	2490	(235.7)
All Noninfectious Events	497	(151.8)	936	(128.4)	1433	(135.7)
All Infections	318	(97.1)	688	(94.4)	1006	(95.2)
Serious Noninfectious Adverse Events	28	(8.6)	31	(4.3)	59	(5.6)
Serious Infections	3	(0.9)	14	(1.9)	17	(1.6)
Grade 3 Noninfectious Adverse Events	29	(8.9)	38	(5.2)	67	(6.3)
Grade 3 Infections	3	(0.9)	12	(1.6)	15	(1.4)
Injections Site Reactions	19	(5.8)	32	(4.4)	51	(4.8)

N = Number of subjects who received at least 1 dose of investigational product.
E = Total number of exposure years
n = Number of Adverse Events
r = Exposure-adjusted event rate per 100 subject years (=n/E*100)

Deaths

In **study 20030117**, two deaths occurred in the placebo/etanercept arm. These were:

- A 47 year old male with a previous history of hypercholesterolaemia and diabetes died of cardiac arrest associated with coronary artery disease 14 months post-initiation of etanercept, during open-label etanercept 50 mg BIW treatment. The cause of death was considered unrelated to etanercept.
- A 64 year old male died of suspected myocardial infarction, 13 months post initiation of etanercept during open-label etanercept 50 mg BIW treatment. He had a history of hyperlipidaemia and a family history of unspecified cardiac disease. The cause of death was considered to be possibly related to etanercept.

In **study 20030115**, one death occurred in the dose escalated arm and one in the non dose escalated arm. These were:

- A 63 year old white female died 3 months after the last dose of etanercept 50 mg BIW of cancer of unknown origin and metastatic cancer. The investigator concluded that the death was unrelated to treatment with etanercept.
- A 67 year old white male, treated with etanercept 50 mg QW and with a previous history of aortic valve replacement, atrial fibrillation, coronary artery disease, hypertension and hypertriglyceridaemia, died 6 months after discontinuing from the study (he had developed a basal cell carcinoma of his left ear). The cause of death was cardiac arrest, which the investigator concluded was not possibly related to treatment with etanercept.

Withdrawals due to adverse events

In **study 20030117**, there were 9 withdrawals in the 12-week double blind period of the study. In the open label period there were 28 subjects withdrawing from the study. Cerebrovascular accidents (2) and breast cancer (2) were the only two adverse events to cause the withdrawal of more than one subject.

In **study 20030115**, there were 21 adverse events responsible for the withdrawal of 20 of 912 subjects. Fifteen of these subjects were in the non dose escalator arm of the study. There was no single adverse event that was responsible for the withdrawal of more than one subject. Eleven of the adverse events (bladder cancer, memory impairment, myelodysplastic syndrome, necrotising granulomatous lymphadenitis, squamous cell carcinoma, sunburn, cardiomyopathy, dizziness, facial infection, myositis, and urticaria) were considered, by the investigator, to be possibly related to etanercept.

Serious Non-infectious Adverse Events (SAEs)

In **study 20030117**, in the 12-week double-blind period of the study, 10 subjects reported at least 1 SAE. Of these only one (hepatic disorder) was considered to be possibly related to study treatment. In the open-label period through Week 96, 47 subjects out of 612 subjects, similarly distributed between the two arms, reported at least 1 SAE. Of the SAEs, tonsil cancer (Day 113), breast cancer (Day 218), impaired healing (Day 243), fracture non-union (Day 225), fistula (Day 299), Hodgkin's disease (Day 411), convulsions (2 subjects: Day 379 and Day 375), myocardial infarction (2 subjects: Day 392 & Day 604) and aggravation of congestive cardiac failure (Day 604) were considered possibly related to etanercept.

In **study 20030115**, of the 912 subjects, 46 subjects reported 59 serious adverse events. All the SAEs were reported once except for myocardial infarction (3), subdural haematoma (2), nephrolithiasis (2), unstable angina (2), chest pain (2), and metastatic lymphoma (2). Of the SAEs, myelodysplastic syndrome (Day 85), necrotising granulomatous lymphadenitis (Day 141), bladder cancer (Day 171), cardiomyopathy (Day 208), hepatic steatosis (Day 351) and squamous cell carcinoma (Day 501) were considered by the investigator to be possibly related to treatment with etanercept.

Serious Infectious Adverse Events

In **study 20030117**, there was one serious infection (perforated appendicitis) in the 12-week double blind period in the placebo arm of the study. This was considered to be unrelated to study treatment. In the open label period of the study through to Week 96, there were 10 subjects who reported serious infectious events. Viral meningitis (Day 464) was the only serious infectious event that was considered possibly related to etanercept treatment by the investigator (Table 16).

In **study 20030115**, there were 12 subjects who reported 17 serious infectious adverse events. Six of the events were considered by the investigator to be possibly related to treatment with etanercept. These were: myositis (Day 261), facial infection (Day 261), septic shock (Day 262), pneumonia (Day 150), cellulitis (Day 335) and pyelonephritis (Day 464).

Table 16: Serious infection by preferred term in descending frequency during open-label period through Week 96 in Study 20030117

Preferred Term	Placebo / Etanercept 50 mg BIW (N = 286) n (%)	Etanercept 50 mg BIW / Etanercept 50 mg BIW (N = 305) n (%)
Number of Subjects Reporting Serious Infectious Adverse Events	7 (2.4)	3 (1.0)
Gangrene	0 (0)	1 (0.3)
Infection	0 (0)	1 (0.3)
Meningitis Viral	0 (0)	1 (0.3)
Cellulitis	2 (0.7)	0 (0.0)
Diverticulitis	1 (0.3)	0 (0.0)
Enteritis Infectious	1 (0.3)	0 (0.0)
Gastroenteritis	1 (0.3)	0 (0.0)
Gastrointestinal Infection	1 (0.3)	0 (0.0)
Localised Infection	1 (0.3)	0 (0.0)

N = Number of subjects who were randomized and received at least 1 dose of open-label investigational product

Clinically significant Adverse Events

Malignancies:

In **study 20030117** (excluding non-melanoma skin cancers) there were two malignancies (pancreatic carcinoma in etanercept arm and bladder carcinoma in placebo arm) reported in the 12-week double-blind period of the study, which were considered by the investigator to be unrelated to etanercept treatment. Of the eight malignancies that were reported in subjects in the open-label period of the study, three were considered by the investigator to be possibly related to etanercept treatment. Of the 3 malignancies only Hodgkin's disease (Day 411) occurred after 48 weeks of treatment (Table 17). The Standardized Incidence Ratios (SIRs) were calculated for all subjects who were randomized and received at least one dose of etanercept using the US NCI's Surveillance Epidemiology and End Results (SEER) program as reference rates. The total number of malignancies in this study was higher than the expected number of events in the general population (SIR = 1.89; 95% confidence intervals [CI]: 0.86, 3.58) (Table 18).

Table 17: Malignancies (Excluding non-melanoma skin cancers) – all etanercept exposure through Week 96 in Study 20030117

Subject	Sex / Age	Study Day Onset	Preferred Term	Study Period	Possibly Related To Investigational Product ?
402013	M / 40	113	Tonsil Cancer	OL	Yes
405008	F / 72	255	B-Cell Small Lymphocytic Lymphoma	OL	No
408006	F / 72	218	Breast Cancer	OL	Yes
415006	F / 55	673	Breast Cancer	OL	No
416018	F / 55	336	Colon Cancer	OL	No
417004	F / 76	249	Adenocarcinoma [a]	OL	No
424006	M / 49	411	Hodgkin's Disease Lymphocyte Predominance Type Stage Unspecified	OL	Yes
436014	F / 64	75	Pancreatic Carcinoma	DB (Etanercept)	No
437013	F / 49	510	Lung Adenocarcinoma Metastatic	OL	No

[a] origin of adenocarcinoma is unknown

Table 18: Standardized Incidence Ratios (SIRs) of malignancies by major organ site – all etanercept exposure through Week 96 in Study 20030117

Malignancy Site	Total Subject Years of Exposure	Observed Number of Events	Expected Number of Events [a]	SIR	95% CI
All Sites[b]	907.3	9	4.77058	1.89	0.86 – 3.58
Oral Cavity and Pharynx	907.3	1	0.1448	6.91	0.17 – 38.48
Leukemia	907.3	1	0.10447	9.57	0.24 – 53.33
Breast	907.3	2	0.55039	3.63	0.44 – 13.13
Digestive System	907.3	3	0.8523	3.52	0.73 – 10.29
Lymphoma	907.3	1	0.2312	4.33	0.11 – 24.10
Respiratory System	907.3	1	0.6615	1.51	0.04 – 8.42

SIR = standardized incidence ratio; CI = confidence interval

[a] Based on Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 13 Regs Public-Use, Nov 2004 Sub for Expanded Races (1992-2002), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2005, based on the November 2004 submission. All races combined, diagnosis dates: 1998-2002, invasive only (except for urinary bladder).

[b] Excluding non-melanoma skin cancer

Fourteen non-melanoma skin cancers were reported in subjects treated with etanercept. Only one of these cancers - basal cell carcinoma on Day 337 - was considered by the investigator to be possibly related to treatment with etanercept. SIRs were calculated for all the subjects

who received at least one dose of etanercept through week 96. The observed events were compared with expected numbers based on two population studies (Arizona and Minnesota). The number of squamous-cell carcinomas in the study through to Week 96 was not statistically significantly different to the Arizona-based data but was statistically significantly higher than the Minnesota-based data. Data for basal-cell carcinoma was not available for the Minnesota study (Table 19).

Table 19: Standardised Incidence Ratios (SIRs) of non-melanoma skin cancers through Week 96 – all etanercept exposure through Week 96 in Study 20030117.

Malignancy Site	Total Subject Years of Exposure	Observed Number of Events [c]	Expected Number of Events [a]	SIR	95% CI
Squamous Cell Carcinoma					
Arizona [a]	907.3	4	2.512	1.59	0.43 – 4.08
Minnesota [b]	907.3	4	1.023	3.91	1.07 – 10.01
Basal Cell Carcinoma - Arizona [a]	907.3	7	10.135	0.69	0.28 – 1.42

SIR = standardized incidence ratio; CI = confidence interval
Events reported in Arizona and Minnesota squamous cell carcinomas are the same events.
[a] Compared to Arizona database. Harris RB et al. (J Am Acad Dermatol 45:528, 2001)
[b] Compared to Minnesota database. Gray DT et al. (Arch Dermatol 133:735-740, 1997)
[c] At the subject level (subject ' experienced 4 basal cell carcinomas at 4 different locations)

In **study 20030115**, there were 7 malignancies reported in 6 subjects. Of these, bladder cancer (Day 171) was the only malignancy considered to be possibly related to etanercept therapy. SIRs were calculated for all the subjects who had received at least one dose of etanercept with cancer incidence rates from the US NCI's Surveillance Epidemiology and End Results (SEER) program as reference rates. The total number of malignancies (excluding non-melanoma skin cancers) was similar to the expected number of events in the general population (SIR = 1.08; 95%CI: 0.40, 2.36).

The total number of skin malignancies (excluding non-melanoma skin cancers) was similar to the general population incidence rates (SIR= 6.91; 95%CI: 0.84, 24.94)

Ten non-melanoma skin cancers were reported. The investigator considered 3 of the squamous cell carcinomas and 1 of the basal cell carcinomas as possibly related to treatment with etanercept. Of these, 2 squamous cell carcinomas (subjects 1593 and 2479) occurred after 48 weeks of etanercept therapy. The observed number of non-melanoma skin cancers was higher than the expected number based on the incidence rates in the Minnesota based study, but were comparable to that based on the Arizona study (Table 20).

Table 20: Standardised Incidence Ratios (SIRs) of non-melanoma skin cancers – All subjects – All exposure in Study 20030115

Malignancy Site	Total Subject Years of Exposure	Observed Number of Events	Expected Number of Events [a]	SIR	95% CI
Squamous Cell Carcinoma					
Arizona [a]	1056.2	5	2.89748	1.73	0.56 – 4.03
Minnesota [b]	1056.2	5	1.17460	4.26	1.38 – 9.93
Basal Cell Carcinoma- Arizona [a]	1056.2	5	11.87625	0.42	0.14 – 0.98

SIR = standardized incidence ratio; CI = confidence interval

Events reported in Arizona and Minnesota squamous cell carcinomas are the same events.

[a] Compared to Arizona database. Harris RB et al. (J Am Acad Dermatol 45:528, 2001)

[b] Compared to Minnesota database Gray DT et al. (Arch Dermatol 133:735-740, 1997)

Injection site reactions (ISRs):

In **study 20030117**, ISRs were more common in the etanercept treated patients than the placebo treated patients (12.2 per 100 subject years of exposure vs 6.1 per 100 subject years of exposure). The largest difference was in injection site erythema.

In **study 20030115**, the EAE rate for dose escalators was slightly lower than that for non dose escalators (4.4 events per 100 subject years of exposure vs 5.8 events per 100 subject years of exposure). The EAE rate in dose escalators before dose escalation was 6.1 events per 100 subject years of exposure compared with 2.9 events per 100 subject years of exposure, after dose escalation. Injection site erythema was the commonest reaction.

Severe (Grade 3) Adverse Events

In **study 20030117**, the incidence of severe adverse events in the placebo arm was higher than that in the etanercept arm (18.2 per 100 subject years of exposure vs 7.6 per 100 subject years of exposure). The most common events were headache, nephrolithiasis, pruritus and shoulder pain.

The incidence of severe infectious adverse events was similar in the two groups. (placebo: 3.0 events per 100 subject years of exposure; etanercept: 2.3 events per 100 subject years of exposure).

In **study 20030115**, the EAE rate of severe non-infectious adverse events was higher in the non dose escalator arm than in the dose escalator arm (8.9 vs 5.2), although the total number of exposure years was similar in the two arms. The most common events (reported more than once) were hypertension, nephrolithiasis, coronary artery disease, subdural haematoma, unstable angina, sciatica and joint sprain.

There was no difference in the EAE rate of severe infectious adverse events in the non dose escalator and dose escalator arms of the study. The only two events reported more than once were cellulitis and abscess.

Adverse Events

In **study 20030117**, the EAE rate for all adverse events through Week 96 was 274 events per 100 subject years of exposure. Headache, injection site bruising, back pain, arthralgia and fatigue were the most common non-infectious adverse events reported in the etanercept arm. Upper respiratory tract infection, nasopharyngitis, sinusitis, influenza and urinary tract

infection were the commonly reported infectious adverse events reported in the etanercept arm (> 6 events per 100 subject years of exposure) (Table 21).

Table 21: All events with at least 5% exposure-adjusted frequency by preferred term in descending frequency through Week 96 in Study 20030117

Preferred Term	Placebo (N = 306) (E = 65.9) n	r	Etanercept 50 mg BIW (N = 598) (E = 908.9) n	r
Total Number of Events	366	(555.3)	2491	(274.1)
Upper Respiratory Tract Infection	16	(24.3)	184	(20.2)
Nasopharyngitis	16	(24.3)	178	(19.6)
Headache	24	(36.4)	85	(9.4)
Sinusitis	4	(6.1)	65	(7.2)
Influenza	6	(9.1)	63	(6.9)
Injection Site Haemorrhage	16	(24.3)	53	(5.8)
Injection Site Erythema	1	(1.5)	48	(5.3)
Back Pain	3	(4.6)	47	(5.2)
Arthralgia	13	(19.7)	44	(4.8)
Urinary Tract Infection	5	(7.6)	41	(4.5)
Diarrhoea	9	(13.7)	34	(3.7)
Gastroenteritis	4	(6.1)	29	(3.2)
Fatigue	6	(9.1)	27	(3.0)
Depression	4	(6.1)	24	(2.6)
Myalgia	10	(15.2)	24	(2.6)
Pain in Extremity	4	(6.1)	23	(2.5)
Insomnia	9	(13.7)	20	(2.2)
Nausea	5	(7.6)	16	(1.8)
Contusion	4	(6.1)	14	(1.5)
Oedema Peripheral	4	(6.1)	14	(1.5)
Skin Laceration	4	(6.1)	14	(1.5)
Back Injury	4	(6.1)	13	(1.4)
Pruritus	7	(10.6)	11	(1.2)
Psoriatic Arthropathy	8	(12.1)	11	(1.2)
Dental Caries	5	(7.6)	5	(0.6)
Pain of Skin	5	(7.6)	1	(0.1)

N = Number of subjects who were randomized and received at least 1 dose of investigational product
E = Total number of exposure years
n = Number of adverse events
r = Exposure-adjusted event rate per 100 subject years (= n / E * 100)

In **study 20030115**, the EAE rate of all events in the study was 236 events per 100 subject years of exposure. The rate of occurrence of all adverse events was no different in the dose escalators compared to the non dose escalators. The most common adverse events in both groups were arthralgia and headache.

The most common infectious adverse events reported were upper respiratory infections, nasopharyngitis, sinusitis, and influenza. Dose escalation did not have any effects on the incidence of infectious adverse events.

Clinical Laboratory Evaluation

In **study 20030117**, there were 12 laboratory abnormalities that were Grade 3 (National Cancer Institute Common Toxicity Criteria – NCI CTC).[9] Nine of these were in the

[9] **Common Toxicity Criteria** is a standardised classification of side effects used in assessing drugs for cancer therapy, in particular. Specific conditions and symptoms may have values or descriptive comment for each level, but the general guideline is 1 – Mild, 2 – Moderate, 3 – Severe, 4 - Life threatening, 5 - Death.

etanercept/etanercept arm and 3 in the placebo/etanercept arm. Of these, six were transient and returned to levels of at least Grade 2. The only one abnormality that was Grade 4 was an elevated alanine transaminase (ALT) in the etanercept/etanercept arm. This subject also had hepatitis B infection.

In all, four subjects withdrew from the study due to abnormal laboratory test results, which were elevated liver function tests, thrombocytopenia, leucocytosis, and leucopenia.

In **study 20030115**, of the 19 laboratory abnormalities that were Grades 3/4, 11 were in non dose escalators and 8 in dose escalators. The two Grade 4 abnormalities (Grade 4 ALT abnormality and Grade 4 anaemia) were in non dose escalators. The Grade 4 ALT abnormality (and the Grade 3 aspartate transaminase [AST] abnormality) returned spontaneously to at least Grade 2 over the next 4 weeks. The Grade 4 anaemia did not respond to withdrawal of etanercept and was ongoing 7 months after cessation of etanercept treatment. Of the Grade 3 abnormalities, eleven subjects had abnormalities in their liver function tests (LFTs) and 5 had abnormal haemoglobin levels (Grade 3 increase in 3 subjects and Grade 3 decrease in 2 subjects). In most subjects the abnormal LFTs were transient.

Antibody status and safety

In **study 20030117**, neutralizing anti-etanercept antibodies were not detected in any of the subjects. Anti-etanercept antibodies were present in 18.3% of the study population. The relationship between the presence of anti-etanercept antibodies and safety was explored. The results showed that anti-etanercept antibodies did not affect safety.

In **study 20030115**, none of the subjects had neutralizing anti-etanercept antibodies. In all 778 of the 908 subjects in the study tested negative for etanercept antibodies. Of the rest (15.2%) who tested positive for etanercept antibodies, 95 tested positive once or twice and 35 tested positive on 3 or more times. The antibody status had no effects on safety. Dose escalation did not influence the antibody status of the subjects.

Safety conclusion

The exposure-adjusted adverse event rates of the two studies were comparable. The reported adverse events were in keeping with the known adverse events associated with etanercept therapy.

There were four deaths reported in the two studies. Only one death from myocardial infarction, 13 months after initiation of treatment with etanercept, was considered to be possibly related to treatment.

In general, the incidence of SAEs in the two studies was low. In study 20030117, there were 11 SAEs possibly related to treatment with etanercept. Of these 5 were reported in the first 48 weeks of the study (carcinoma of the tonsil, carcinoma of breast, impaired healing, fracture non-union and fistula) and 6 were reported in the second 48 weeks of the study (Hodgkin's disease, convulsions x 2 subjects, myocardial infarction x 2 subjects, and congestive cardiac failure). In study 20030115, of the five SAEs that were possibly related to etanercept therapy, squamous cell carcinoma was the only SAEs reported after 48 weeks.

The incidence of serious infectious adverse events appears not to have increased after 48 weeks of therapy with etanercept. In study 20030117, of the 10 reported serious infectious events, viral meningitis was the only event considered to be possibly related to etanercept therapy and was reported after 48 weeks of treatment. In study 20030115, there were six serious infectious adverse events that were considered by the investigator to be possibly

related to etanercept therapy. Of these, only one (pyelonephritis) was reported after 48 weeks of therapy.

Similarly, there was no increase in the incidence of malignancies beyond 48 weeks of therapy. In study 20030117, of the 3 malignancies that were considered to be related to etanercept therapy, only Hodgkin's disease (Day 411) was reported after 48 weeks. Of the 14 non-melanoma skin cancers that were reported, only a basal cell carcinoma at 48 weeks was considered to be possibly related to etanercept therapy. In study 20030115, there were no malignancies attributable to etanercept therapy reported, except for 4 non-melanoma skin cancers, of which a squamous cell carcinoma and a basal cell carcinoma were reported after 48 weeks.

The incidence of Grade 4 liver function abnormalities was small. These abnormalities were either transient or were associated with liver disease. The Grade 3 abnormalities were in the main transient. Overall, there was no biochemical or haematological toxicities apparent. Neutralizing anti-etanercept antibodies were not detected in these studies. Anti-etanercept antibodies did not impact on the safety of treatment with etanercept.

Clinical Summary and Conclusions

The objective of this application was to demonstrate the efficacy, safety and tolerability of etanercept 50 mg, either as once weekly (QW) or twice weekly (BIW) dosing regimens in subjects with psoriasis, over a period up to 96 weeks.

Etanercept provided statistically significant improvement to subjects with plaque psoriasis.

- The PASI 75 response in study 20030117 was achieved by 47% of those treated with etanercept and 5% of those treated with placebo at Week 12. Following initiation of etanercept therapy in the placebo arm, almost two thirds of the subjects in both arms had achieved PASI 75 at the Week 48 visit.
  The improvement was maintained through Week 96, albeit with some decline in PASI 75 response in both arms between Weeks 48 and 96. This decline was considered to be partly due to subject non-compliance with etanercept therapy.
- In study 20030115, the PASI 50, 75 and 90 responses at 48 weeks were maintained through to Week 72.
- The other measures of efficacy (sPGA, and DLQI) had similar outcomes. Etanercept therapy had a continued beneficial effect on the symptoms of depression and fatigue as measured by the HAM-D scale, the BDI scoring system and the FACIT fatigue scale through to Week 72.

The safety of etanercept 50 mg QW/BIW over a period up to Week 96 was examined. The EAE rate in study 20030117 (up to 96 weeks) was similar to the EAE rate in the two arms of study 20030115 (up to 72 weeks). This would suggest that the safety profile of etanercept therapy remained unchanged up to 96 weeks. Similarly, as demonstrated in study 20030115, the safety profile was not affected by dose escalation. The reported adverse events, including serious adverse events, were in keeping with the known adverse events associated with etanercept therapy.

The safety data demonstrated that the incidence of adverse events, and in particular, the incidence of malignancy and serious infections, did not increase over the second 48 weeks of etanercept therapy.

Recommendation

The evaluator recommended that the application for extension of indication to include 'the treatment of adult patients with moderate to severe chronic plaque psoriasis, who are candidates for phototherapy or systemic therapy' should be approved, provided a statement to the effect that 'safety and efficacy beyond 96 weeks have not been demonstrated' is included in the proposed product information (PI).

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There is no requirement for a quality evaluation in an application of this type.

Nonclinical

There is no requirement for a nonclinical evaluation in an application of this type.

Clinical

The clinical evaluator has recommended approval of the revised indication.

The sponsor has submitted two studies to support the long term efficacy and safety of etanercept in the treatment of psoriasis.

Study 117 consisted of two phases:

- An initial 12-week, randomised, double-blind comparison of etanercept versus placebo;
- An 84-week, open-label, extension phase.

Subjects therefore received up to 96 weeks (~ 2 years) of treatment in the trial.

Study 115 was an open-label extension study for patients who had completed one of two earlier Phase III trials (study 1639 or study 1642) which were evaluated by the TGA in the original application for the psoriasis indication. Once enrolled in study 115, subjects could receive up to 72 weeks (~ 18 months) of additional etanercept treatment.

Following completion of the clinical evaluation, the sponsor was requested to provide further analysis of the safety data from the two studies. The sponsor's response was considered by the Delegate and the Australian Committee on Prescription Medicines.

Pharmacokinetics

In study 117, trough levels of etanercept were monitored. There was no notable change in these levels between week 12 and week 96.

Efficacy

In **study 117**, the primary efficacy endpoint was the proportion of patients who achieved a 75% improvement in the Psoriasis Area and Severity Index (PASI) score. This has been the standard efficacy measure for all biological agents for psoriasis that have been reviewed by the TGA and ADEC in recent years.

Results for the PASI 75 endpoint are shown in Figure 2. Efficacy was largely maintained between weeks 48 and 96, although there was some decrease during this period which was felt to be due in part to a lack of compliance with treatment. There were a number of secondary efficacy endpoints, which gave similar findings.

In **study 115**, demonstration of maintenance of efficacy was a secondary objective for the trial. For the period between 48 and 72 weeks, there was again a modest decrease in the proportion of patients who maintained a 75% improvement in PASI score, although the proportion remained well above that observed at baseline.

Safety

In study 117, a total of 464 subjects completed the 96 weeks (2 years) of trial therapy. In study 115, a total of 485 subjects completed 72 weeks (18 months) of treatment. These long-term exposure patient numbers compare favourably with data provided for the other biological agents in psoriasis as summarised in the Table 22.

Table 22: Long-Term Exposure for Biological Agents Used to Treat Psoriasis

	> 18 months	**> 24 months**	**> 30 months**
Alefacept	554	362	171
Adalimumab	163	142	-
Ustekinumab	373	-	-
Etanercept	949*	464	-

*464 + 485

The pattern of toxicity observed in the two studies was consistent with that previously seen with etanercept.

A concern with the long-term use of immunosuppressive agents such as etanercept is the potential for the development of malignancies. In study 117, there was a non-significant increase in the incidence of malignancies compared to the expected number based on historical data - Incidence Ratio 1.89; 95% CI: 0.86 – 3.58 (Table 18). In study 115, there was no suggestion of an increased risk - Incidence Ratio 1.08; 95% CI: 0.40 – 2.36. In terms of squamous cell carcinoma of the skin, there were conflicting results in both studies depending on the historical database used for comparison. There was no suggestion of an increased risk of basal cell carcinoma.

In their response to the clinical evaluation, the sponsor has provided an analysis of the incidence of adverse events over time. There was no suggestion that increasing exposure was associated with increasing incidence of adverse events.

Risk-Benefit Analysis

Overall risk-benefit with long-term use

The submitted studies provide evidence of maintenance of efficacy when etanercept is administered for up to 2 years. No new safety issues have been documented with such use and there is no evidence of cumulative increase in toxicity. The potential for an increased incidence of malignancy is a known risk and is addressed through appropriate warnings in the product information. The Delegate considered the risk-benefit ratio of long-term use to be favourable and he proposed to approve the application.

Use beyond 2 years

The clinical evaluator recommended that a statement be included in the 'Clinical Trials' section of the PI to the effect that safety and efficacy have not been demonstrated beyond 96 weeks. The Delegate did not propose to enforce this requirement as it was not required for alefacept or adalimumab, both of which provided data out to 2 years.

Product Information

The 'Clinical Trials' section should include a brief description of the results of study 117, with emphasis on the efficacy findings between 48 and 96 weeks.

Advisory Committee

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

ACPM recommended approval of the submission for the removal of the text "*Safety and efficacy beyond 12 months have not been demonstrated"* from the current psoriasis indication for etanercept.

In making this recommendation, the ACPM agreed with the Delegate that the submitted studies provided evidence of maintenance of efficacy when etanercept is administered for up to 2 years. No new safety issues have been documented with such use and there is no evidence of cumulative increase in toxicity. The potential for an increased incidence of malignancy is a known risk and is adequately addressed through appropriate warnings in the product information.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Enbrel powder for injection vial with diluent syringe composite pack and solution for injection pre-filled syringe containing etanercept *rch* 25mg, 50mg powder for injection and 25mg, 50mg solution for injection for the revised indication:

Treatment of adult patients with moderate to severe chronic plaque psoriasis, who are candidates for phototherapy or systemic therapy.

Attachment 1. Product Information

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

DESCRIPTION
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.

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.

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
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.

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).

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.

Geriatric patients
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.

CLINICAL TRIALS
This section presents data from 5 randomised controlled trials in rheumatoid arthritis, 1 study in polyarticular JIA, 2 trials in ankylosing spondylitis, 1 trial in psoriatic arthritis and 2 trials in 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. By definition, an ACR 20 response is achieved if a patient experiences a 20% improvement in their tender joint count and swollen joint count plus ≥ 20% improvement in at least three of the following five criteria: (1) patient pain assessment, (2) patient global assessment, (3) physician global assessment, (4) patient self-assessed disability and (5) acute-phase reactant (erythrocyte sedimentation rate or C-reactive protein). ACR 50 and 70 responses are defined using the same criteria with a 50% improvement or a 70% improvement, respectively. 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.

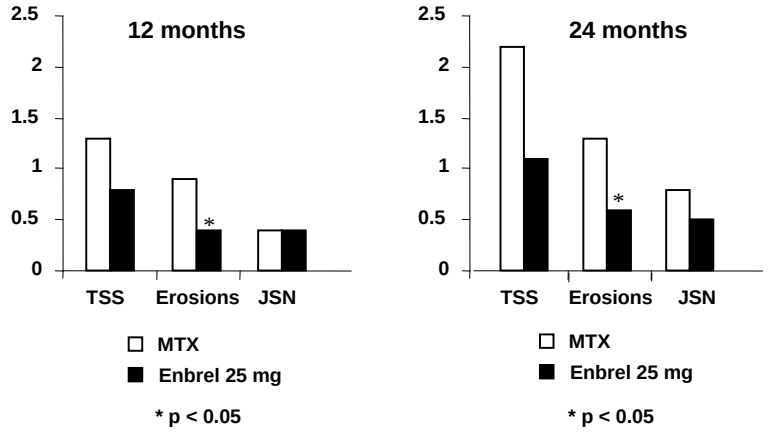
The safety and efficacy of 50 mg ENBREL (two 25 mg SC injections) administered once weekly were evaluated in a double-blind, placebo-controlled study of 420 patients with active RA. In this study, 53 patients received placebo, 214 patients received 50 mg ENBREL once weekly and 153 patients received 25 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 12.9mg/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% $^{\dagger,\phi}$
Week 52	75.0%	75.8%	84.8% $^{\dagger,\phi}$
ACR 50 Response			
Week 24	40.8%	40.4%	59.3% $^{\dagger,\phi}$
Week 52	42.5%	48.4%	69.3% $^{\dagger,\phi}$
ACR 70 Response			
Week 24	15.4%	17.0%	35.9% $^{\dagger,\phi}$
Week 52	18.9%	24.2%	42.9% $^{\dagger,\phi}$
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

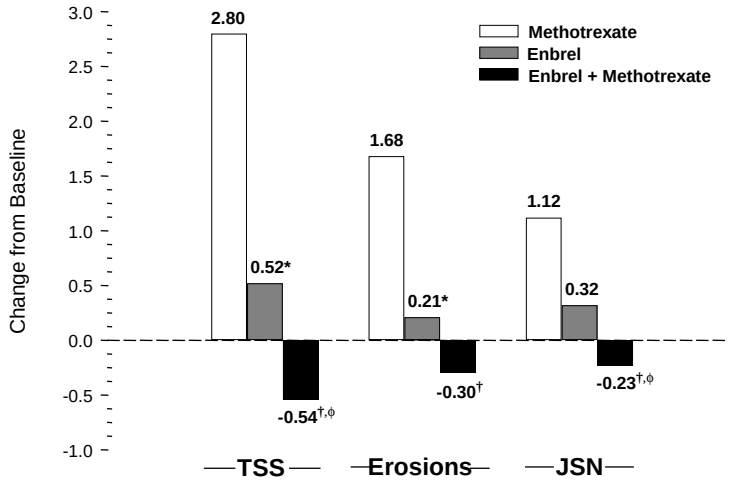
The percentage of patients who achieved low disease activity (defined as DAS < 2.4) at 52 weeks was 39%, 35% and 61% for patients in the ENBREL alone group, methotrexate alone group and the ENBREL

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 and etanercept, 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).

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 at week 8 in their effect on signs and symptoms of RA.

Safety, efficacy and immunogencity 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. 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 JIA Definition of Improvement (DOI), 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.

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 ≤25mg/week methotrexate. Doses of 25mg 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 (n = 62)	**ENBREL[a] (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 etanercept in the open-label part, further radiographic progression was inhibited after subjects began receiving etanercept. 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.

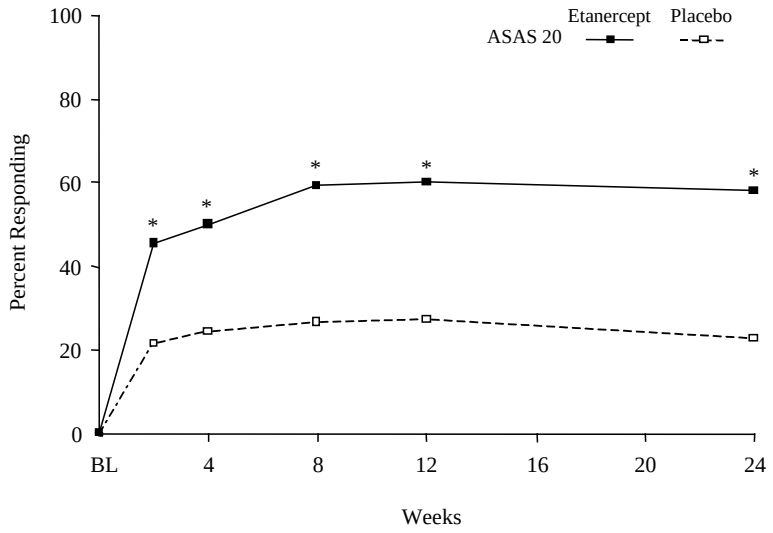
Quality of life in psoriatic arthritis patients was assessed using the Health Assessment Questionnaire (HAQ) and SF-36 instruments. There was a statistically significant improvement in mean HAQ score from 1.1 to 0.5 on a scale of 0 to 3 for patients treated with ENBREL. The SF-36 showed improvements 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
Response	n = 166 wk 12	n =162 wk 12	n =162 wk 24[a]	n = 164 wk 12	n = 164 wk 24[a]	n = 193 wk 12	n = 196 wk 12	n = 196 wk 12
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 ≤ 0.0001 compared with placebo

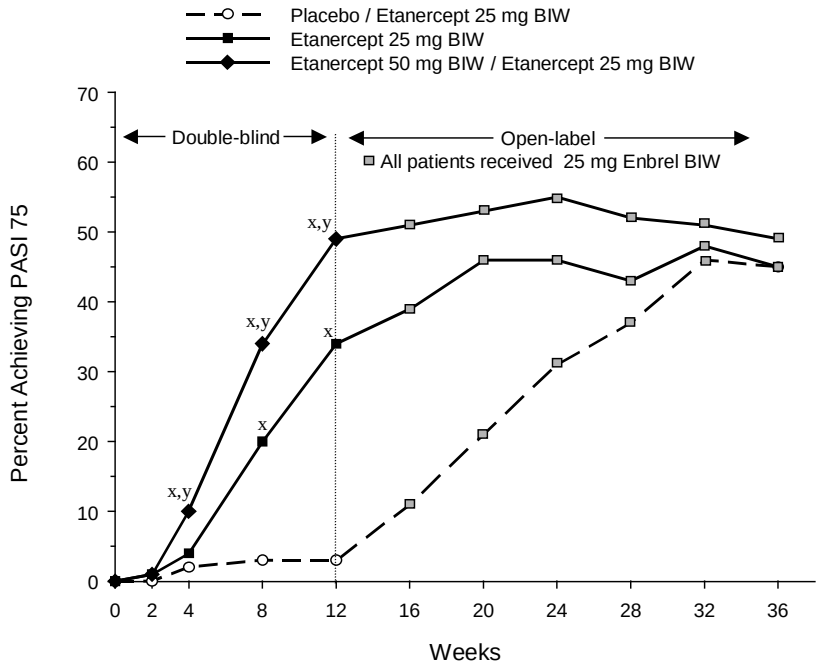
a No statistical comparisons to placebo were made at week 24 in Study 1 because the original placebo group began receiving ENBREL 25 mg BIW from week 13 to week 24.

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.

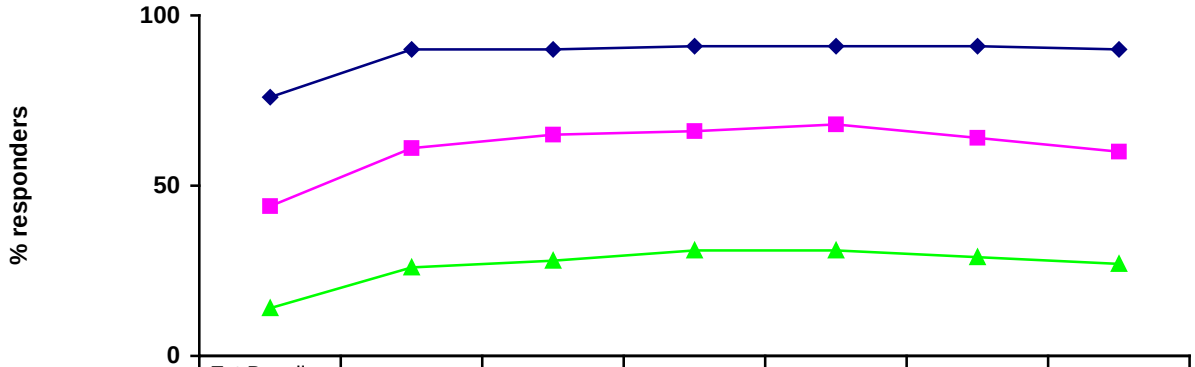
PASI 75 Response of Patients with Plaque Psoriasis in Study 2



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 50mg 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 esponders from parent study baseline (LOCF) in patients receiving ENBREL 50 mg once weekly.

ENBREL 50mg 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.

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 JCA 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 1084 patients developed antibodies to ENBREL, none were neutralising.

INDICATIONS
ENBREL is indicated for the treatment of:
- 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, adult rheumatoid arthritis to slow progression of disease-associated structural damage in patients at high risk of erosive disease (see Clinical Trials).
- Active polyarticular-course juvenile idiopathic arthritis in patients (4 to 17 years) who have had inadequate response to one or more disease-modifying anti-rheumatic drugs. ENBREL has not been studied in children less than 4 years of age.
- 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).
- The signs and symptoms of active ankylosing spondylitis in adults.
- Treatment of adult patients with moderate to severe chronic plaque psoriasis, who are candidates for phototherapy or systemic therapy.

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. Some of these infections have been fatal. These infections were due to bacteria, mycobacteria, fungi and viruses. Opportunistic infections have also been reported. Many of these serious events have occurred in patients with underlying diseases that, in addition to their RA, could predispose them to infections. 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 atypical mycobacterium infection) or sepsis.

Opportunistic infections, including invasive fungal infections, have been reported in patients receiving etanercept. In some cases, fungal and other opportunistic infections are not recognised and this has resulted in delays in approriate treatment, sometimes resulting in death. In many of the reports, patients have also received concomitant medicines including immunosuppressants. 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 mycobacterium infection including mycobacterium avium complex in patients on treatment with etanercept 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 virus (HBV) in patients who are chronic carriers of this virus who are receiving TNF blockers including ENBREL has been reported. A causal relationship has not been established for ENBREL. 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 identified as carriers of HBV. Patients who are carriers of 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 etanercept 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) 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.

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. This combination has not demonstrated increased clinical benefit; such use is not recommended.

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) and also 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.

Cardiac disorders
There have been post-marketing reports of worsening of congestive heart failure (CHF), with and without identifiable precipitating factors, in patients taking etanercept. Two large clinical trials evaluating the use of etanercept 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 in those patients assigned to etanercept treatment. Physicians should use caution when using etanercept in patients who also have CHF.

CNS disorders
Although no clinical trials have been performed evaluating etanercept 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). A careful risk/benefit evaluation, including a neurological assessment, is recommended when prescribing etanercept 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
The safety and efficacy of etanercept in combination with other immunosuppressive agents used in psoriasis or with phototherapy have not been studied. Etanercept 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.

Immunosuppression and malignancy
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 4509 ENBREL-treated patients versus 0 among 2040 control patients (duration of controlled treatment ranged from 3 to 24 months). In the controlled and open-label portions of clinical trials of ENBREL, 9 lymphomas were observed in 5723 patients over approximately 11201 patient-years of therapy. This is 3-fold higher than that expected in the general population. 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.

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.

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.

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.

Non-melanoma skin cancer has been reported in patients treated with TNF-antagonists including ENBREL. 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. Periodic skin examination is recommended for all patients who are at risk for non-melanoma skin cancer.

Paediatric patients
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.

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.

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. 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 in agreement with current immunisation guidelines prior to initiating ENBREL therapy.

Autoantibody formation
Treatment with ENBREL may result in the formation of autoimmune antibodies (see ADVERSE EFFECTS).

Genotoxicity and effects on fertility
Genotoxicity studies showed no evidence of gene mutations or chromosomal damage. Long-term animal studies have not been conducted to evaluate the carcinogenic potential of ENBREL or its effects on fertility.

Use in pregnancy
Category B2
The safe use of etanercept 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.

Use in lactation
The safe use of etanercept during lactation has not been established. It is not known whether etanercept is excreted in human milk or absorbed systemically after ingestion. There are no animal studies assessing the effects of ENBREL on the neonate. Because many drugs and immunoglobulins are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ENBREL, a decision should be made whether to discontinue nursing or discontinue the drug.

Use in children
ENBREL has not been studied in children less than 4 years of age.

Studies have not been done in patients with polyarticular-course JIA to assess the effects of continued ENBREL therapy in patients who do not respond within 3 months of initiating ENBREL therapy or to assess the combination of ENBREL with methotrexate.

The safety and efficacy of ENBREL in paediatric patients (i.e. <18 years) with chronic plaque psoriasis have not been established.

Use in the elderly
A total of 123 RA patients aged 65 years or older have been studied in clinical trials. No overall differences in safety or effectiveness were observed between these patients and younger patients. Greater sensitivity of some older individuals cannot be ruled out.

Interactions with other medicines

Methotrexate
ENBREL may be administered in combination with methotrexate for the treatment of rheumatoid arthritis. In a safety and efficacy clinical trial, methotrexate had no effect on the pharmacokinetics of etanercept. The effect of ENBREL on the human pharmacokinetics of methotrexate has not been investigated. The safety and efficacy of etanercept in combination with methotrexate for the treatment of psoriasis have not been studied. ENBREL should not be administered in combination with methotrexate for the treatment of psoriasis (See PRECAUTIONS). Product Information for methotrexate should be consulted when etanercept is administered with methotrexate.

Anakinra
Patients treated with ENBREL and anakinra were observed to have a higher rate of serious infection when compared with patients who were treated with ENBREL alone (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).

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 etanercept 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 $_{(0-t)}$ (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 $_{(0-t)}$ (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.

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.

Ability to drive or operate machinery

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

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 or swelling) compared with placebo-treated patients. 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 etanercept therapy.

Infections

Serious and fatal infections have been reported; reported pathogens include bacteria, mycobacteria, viruses and fungi. Opportunistic infections have also been reported. Mycobacterium infections include tuberculosis (incidences are rare) and atypical mycobacterium infection (including mycobacterium avium complex).

In clinical trials in rheumatic disorders, upper respiratory infections ("colds") and sinusitis were the most frequently reported infections in patients receiving ENBREL or placebo. In placebo-controlled trials, the incidence of upper respiratory tract infections was 17% in the placebo treatment group and 22% in the group treated with ENBREL. In rheumatoid arthritis patients participating in placebo controlled trials, there were 0.68 events per patient year in the placebo group and 0.82 events per patient year in the group treated with ENBREL when the longer observation of patients on ENBREL was accounted for.

In controlled trials in patients with rheumatoid arthritis, the rates of reported serious (fatal, life-threatening, or required hospitalisation or intravenous antibiotics) and non-serious infection were similar for ENBREL and placebo when adjusted for duration of exposure. Some infections 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. (See PRECAUTIONS). Data from a sepsis clinical trial in patients with established sepsis suggest that ENBREL treatment may increase mortality in these patients.

In placebo-controlled psoriatic arthritis and plaque psoriasis trials of up to 24 weeks duration, there were no differences in rates of infection among patients treated with ENBREL and those treated with placebo. In the double-blind and open-label psoriatic arthritis trials, one patient reported a serious infection (pneumonia). The risk of infection with long-term treatment cannot be estimated from this data.

Malignancies
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 4462 rheumatoid arthritis patients treated with ENBREL in clinical trials for a mean of 27 months (approximately 10000 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**:** Immunosuppression and malignancy).

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

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. 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 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.

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
Infections and Infestations	
Very Common	Infections (including upper respiratory tract infections, bronchitis, cystitis, skin infections)*
Common	Serious infections (including pneumonia, cellulitis, septic arthritis, sepsis)*
Rare	Tuberculosis
Immune System Disorders	
Common	Allergic reactions; autoantibody formation
Rare	Serious allergic/anaphylactic reactions (including angioedema, bronchospasm)
Not known	Macrophage activation syndrome, ANCA positive vasculitis
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
Eye Disorders	
Uncommon	Uveitis**
Skin and Subcutaneous Tissue Disorders	
Very Common	Injection site reactions
Common	Pruritus
Uncommon	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	
Rare	Elevated liver enzymes, autoimmune hepatitis

*see additional information, under “Infections” above.

** Uveitis has been reported in clinical trials and post-marketing experience. The reported frequency for placebo-treated patients in clinical trials was similar to the reported frequency for etanercept-treated patients.

*** See additional information under “Psoriasis” above.

Paediatric patients with juvenile idiopathic arthritis

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

JIA patients treated with ENBREL has 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 clinical trials, two cases of varicella infection with signs and symptoms suggestive of aseptic meningitis have been reported among JIA patients treated with ENBREL.

There were 4 reports of macrophage activation syndrome in JIA clinical trials.

DOSAGE AND ADMINISTRATION

Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, psoriatic arthritis, psoriasis or ankylosing spondylitis. 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 with juvenile idiopathic arthritis

The recommended dose for children 4-17 years of age is 0.4 mg/kg (up to a maximum of 25 mg) after reconstitution of 25 mg ENBREL in 1 mL of water for injections, given twice weekly as a subcutaneous injection with an interval of 3-4 days between doses.

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. Sites for self-injection include thigh, abdomen, or upper arm.

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 injection, ENBREL single-use Auto-injector should be allowed to reach room temperature (15-30 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.

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

PRESENTATION
Powder for injection
ENBREL powder for injection contains either 25 mg or 50 mg of etanercept. 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.

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). Eight 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. 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 4, 8 or 24 alcohol swabs.
* not marketed

Poison Schedule
S4, PRESCRIPTION ONLY MEDICINE.

Storage
Powder for injection
Store at 2ºC to 8°C. Refrigerate. Do not freeze. The solution should be used immediately (i.e. within 6 hours) after reconstitution. If not used immediately, ENBREL solution must be refrigerated in the vial at 2°C to 8°C after reconstitution.

Solution for injection and Auto-injector
Store at 2ºC to 8°C. Refrigerate. Do not freeze. Keep the pre-filled syringes and the Auto-injectors in the outer carton in order to protect from light.

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