



Australian Government

Department of Health and Ageing  
Therapeutic Goods Administration

# Australian Public Assessment Report for Etanercept

Proprietary Product Name: Enbrel

Sponsor: Pfizer Australia Pty Ltd

**March 2012**

**TGA** Health Safety  
Regulation

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- 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.

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## I. Introduction to Product Submission

### Submission Details

<i>Type of Submission</i>	Extension of indications
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	22 December 2011
<i>Active ingredient(s):</i>	Etanercept
<i>Product Name(s):</i>	Enbrel
<i>Sponsor's Name and Address:</i>	Pfizer Australia Pty Ltd 38-42 Wharf Rd, West Ryde NSW 2114
<i>Dose form(s):</i>	Powder for Injection Solution for injection
<i>Strength(s):</i>	25 mg and 50 mg (vial and pre-filled syringe) 50 mg (auto-injector)
<i>Container(s):</i>	Glass vial (powder for injection only) Glass pre-filled syringe (Solution for injection) Glass pre-filled syringe in Auto-injector (Solution for injection)
<i>Pack size(s):</i>	Four.
<i>Approved Therapeutic use:</i>	Treatment of chronic, severe plaque psoriasis in children and adolescents from age 4 to 17 years, who are inadequately controlled by, or are intolerant to, other systemic therapies or photo therapies. Duration of therapy to be no longer than 24 weeks and treatment to be ceased after 12 weeks if a significant PASI response is not achieved.
<i>Route(s) of administration:</i>	Subcutaneous (SC) injection
<i>Dosage:</i>	0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly.
<i>ARTG Number (s)</i>	90456, 107316, 124421, 124422, 157622

### 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. 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. 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.

Etanercept is currently approved in Australia for a number of indications, including the treatment of psoriasis in adults. The approved adult psoriasis indication is:

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

The approved dosage regimen for adult psoriasis patients is 50 mg once weekly or 25 mg twice weekly. A higher dose of 50 mg twice weekly may be used for the initial 12 weeks of treatment in adults

This AusPAR describes the sponsor’s application to extend its use in psoriasis to include: Treatment of chronic, moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies

No limit on treatment duration was proposed by the sponsor.

In recent years the TGA has approved several biological agents for the treatment of psoriasis. None of these therapies have been approved for use in children.

### Regulatory Status

The regulatory status of Enbrel is summarised in Table 1 below.

**Table 1. Enbrel. Paediatric Psoriasis Indication) as of 3 November 2011.**

Market	Approval date
Europe	Original filing: 22 December 2008 Second filing (6-7 year olds): 24 August 2011
USA	Withdrawn August 2009*
Canada	Withdrawn August 2009*
Switzerland	Original filing: 12 October 2010 Second filing (6-7 year olds): Positive preliminary decision received on 7 October 2011

\*A number of post approval studies were requested which the sponsor were unable to conduct, due to the difficulty in recruiting enough patients to give the study sufficient statistical power.

### Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

## II. Quality Findings

There was no requirement for a quality evaluation in a submission of this type.

## III. Nonclinical Findings

There was no requirement for a nonclinical evaluation in a submission of this type.

## IV. Clinical Findings

### Introduction

The sponsor has performed a development program with the intention of demonstrating efficacy and safety for etanercept for paediatric patients aged 4 to 17 years with moderate to severe plaque psoriasis. Etanercept is currently approved for the treatment of 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. However, the sponsor is applying for the new indication in children 6 years and over but not for the 4 year and 5 year age groups.

Study 20030211 and Study 20050111 are both stated to have been conducted according to Good Clinical Practice (GCP).

### Pharmacokinetics

Limited pharmacokinetic data were provided from Study 20030211.

Study 20030211 was a multicentre, randomised, double blind, parallel group, placebo controlled clinical trial conducted in 211 children and adolescents aged 4 to 17 years. No formal pharmacokinetic or pharmacodynamic analyses were undertaken on this data.

The trough plasma concentrations reported are reassuring that the proposed dosing in children results in a similar level of exposure to that for adults given the adult dosing schedule.

### Efficacy

Efficacy data were provided from one pivotal study (Study 20030211) and one supportive study (Study 20050111).

#### Study 20030211

##### *Methods*

Study 20030211 was a multicentre, randomised, double blind, parallel group, placebo controlled clinical trial. The study was conducted at 30 sites in the USA and 12 sites in Canada.

The inclusion criteria included:

- Aged 4 to 17 years, inclusive.
- History of psoriasis for  $\geq 6$  months at the time of randomisation.
- Must meet either of the following criteria:
  - Current or past treatment with phototherapy or systemic psoriasis therapy (methotrexate, cyclosporin, retinoids).
  - Poorly controlled with topical psoriasis therapy as evidenced by persistence of moderate to severe psoriasis despite a current or previous treatment course of at least 6 week duration with a corticosteroid of at least moderate potency or a Vitamin D analog. Persistent moderately severe psoriasis during the treatment course was defined as signs and symptoms of psoriasis listed as follows, occurring over a clinically significant portion of the body surface area (BSA), in the opinion of the investigator:
    - Erythema: at least moderate red coloration.
    - Induration: at least moderate plaque elevation with rounded or sloped edges.

- Scaling: at least coarse scaling.
- During the screening period, must have had stable moderate to severe plaque psoriasis, as defined by:
  - Stable moderate to severe plaque psoriasis.
  - Static Physician's Global Assessment of Psoriasis (sPGA) score of  $\geq 3$  (moderate).
  - Involvement of  $\geq 10\%$  of the BSA.
  - Psoriasis Area and Severity Index (PASI)<sup>1</sup> score of  $\geq 12$ .
- Must have had an updated immunisation schedule according to the American Academy of Pediatrics guideline in the US or the Canadian Immunization Guide in Canada to minimize the need for immunisation during the study treatment period.
- Female subjects of childbearing potential must have had negative serum test at screening and a urine pregnancy test at Day 1.
- Sexually active male and female subjects had to practice an effective method of birth control.

The exclusion criteria included:

- Presence of guttate, erythrodermic or pustular psoriasis during the screening period.
- Any Grade 3 or 4 adverse event (AE), infection, or laboratory toxicity based on the Common Toxicity Criteria (CTC)<sup>2</sup> version 2.0 at the time of the screening visit or between the screening visit and initiation of investigational product administration
- Any Grade 3 or 4 infection within 30 days before the first screening visit or during the screening period.
- Any chronic or recurrent active infection within 6 months of screening.
- Evidence of skin conditions (such as eczema) at the time of the screening visit that would interfere with evaluations of the effect of investigational product on psoriasis.
- Psoralen ultraviolet A phototherapy (PUVA), ultraviolet B (UVB) photo therapies, and ultraviolet A phototherapy (UVA) within 14 days before the first dose of investigational product.
- Receipt of systemic biologic agents (such as Raptiva [efalizumab], Amevive [alefacept]) within 30 days before the first dose of investigational product.
- Receipt of any other systemic psoriasis therapy (such as methotrexate, ciclosporin) or oral parenteral corticosteroids within 14 days before the first dose of investigational product.
- Topical steroids, topical Vitamin A or D analogue preparations, anthralin or calcineurin inhibitor within 14 days before the first dose of investigational product

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<sup>1</sup> This is a widely used tool for the measurement of severity of psoriasis. PASI combines the assessment of the severity of lesions and the area affected into a single score in the range 0 (no disease) to 72 (maximal disease).

<sup>2</sup> Common Terminology Criteria (CTC) 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.

(with the exception of topical steroids at no higher than moderate strength on the scalp, axillae and groin).

- Previous receipt of etanercept or any other anti-TNF agent(s).
- Receipt of live attenuated vaccine (such as measles-mumps-rubella (MMR) or varicella) within 12 weeks before the first dose of investigational product, or intranasal influenza vaccine.
- Current use of medication known to aggravate psoriasis (such as lithium).
- Pregnant or breast feeding.
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 times the upper limit of normal (ULN) for the age range.
- Creatinine >1.5 times ULN for the age range.
- White blood cell count <2.0 x 10<sup>9</sup>/L and/or a neutrophil count <1.5 x 10<sup>9</sup>/L.
- Hemoglobin <8.5 g/dL.
- Platelet count <150 x 10<sup>3</sup>/L.
- Significant concurrent medical conditions, which included:
  - uncontrolled, clinically significant systemic disease at screening (hepatic, renal, neurological, endocrine, cardiac, gastrointestinal, or hematological disease)
  - diagnosis of multiple sclerosis or any other demyelinating disease
  - insulin dependent diabetes mellitus
  - history of cancer
  - known human immunodeficiency virus, hepatitis B virus infection, or hepatitis C virus infection
  - any condition that might cause the study to be detrimental to the subject, in the judgment of the investigator
- Any evidence of cutaneous basal or squamous cell carcinoma or melanoma during screening.
- Current or history of psychiatric, addictive, or any other disorder that could have compromised the ability of the subject, parent, or legal guardian to give informed consent and/or assent, as appropriate for the subject's participation in the study.
- Current or history of alcohol or drug abuse by the subject, parent or legal guardian that could have interfered with the ability to comply with the study protocol.

The study treatments were:

1. Etanercept 0.8 mg/kg up to a maximum dose of 50 mg, once weekly by subcutaneous (SC) administration
2. Placebo

There was a 12 week double blind, placebo controlled treatment phase, followed by a 24 week open label phase, followed by a 12 week randomised double blind withdrawal phase (48 weeks in total). Etanercept was supplied as a sterile lyophilized powder in vials containing 25 mg etanercept. Treatment allocation was by Interactive Voice Response



(IVRS), with block randomisation and stratification by age group 4 to 11 years and 12 to 17 years.

Subjects were not to receive the following therapies throughout the duration of the study, including the 30 day follow up period:

- PUVA, UVA, or UVB therapy.
- Any systemic psoriasis therapy.
- Oral or parenteral corticosteroids including intramuscular or intra articular administration (the use of otic, nasal, or inhaled corticosteroids within recommended doses was allowed).
- Topical steroids, topical Vitamin A or D analog preparations or anthralin. The use of topical steroids that are low or moderate potency was allowed during the study on the scalp, axilla, and groin only. At the investigator's discretion, the use of topical steroids of mild potency was allowed on the face. Topical standard of care, including those listed above, was allowed for subjects who entered the incomplete-responder arm
- Topical calcineurin inhibitors (allowed for subjects who entered the incomplete responder arm)
- Kineretã (anakinra)
- Excessive sunbathing or use of tanning salons

The primary efficacy outcome measure was the PASI 75 response at Week 12. A PASI 75 response was defined as a 75% or greater decrease from baseline in PASI score. The secondary efficacy outcome measures were:

- PASI 50 response at Week 12
- Clear/almost clear status of sPGA at Week 12.
- Percent improvement from baseline in Children's Dermatology Life Quality Index (CDLQI) at Week 12.
- PASI 90 response at Week 12

The following additional endpoints were included in the protocol:

- PASI 50, PASI 75, and PASI 90 response at each scheduled visit week except Week 12.
- Percent improvement from baseline in PASI score at each scheduled visit week.
- Clear/almost clear status of sPGA at each scheduled visit week except Week 12.
- Clear status of sPGA at each scheduled visit week.
- sPGA at each scheduled visit week.
- Percent improvement from baseline in the CDLQI at each scheduled visit week except Week 12.
- Percent improvement from baseline in the CDLQI sub scales at each scheduled visit week.
- Improvement from baseline in joint pain at each scheduled visit week.

- Improvement from baseline in the photograph derived Nail Psoriasis Severity Index (NAPSI) at each scheduled visit week.
- Improvement from baseline in the Stein Impact on Family scale at each scheduled visit week.
- Improvement from baseline in the Pediatric Quality of Life (Peds QL) total score, 2 summary scores and 4 sub scales at each scheduled visit.
- Improvement from baseline in the Harter's Self-perception Profile for Children total score and 6 sub-scales at each scheduled visit.
- Improvement from baseline in Harter's Self-perception Profile for Adolescents total score and 9 subscales at each scheduled visit.
- Time to loss of PASI 75 response for all PASI 75 responders who enter the randomised double blind withdrawal period at Week 36.

The safety endpoints were: Adverse Events (AEs), infectious episodes, injection site reactions, laboratory toxicity, vital signs, antibodies to etanercept and disease rebound during the randomised double blind withdrawal period (defined as a post baseline PASI score that was > 125% of baseline PASI within 3 months of treatment discontinuation).

### ***Statistical Issues***

Hypothesis tests for categorical efficacy endpoints were performed using the Cochran-Mantel-Haenszel (CMH) test, with age group as the stratification factor. For categorical outcomes analysed by age subgroups, the Pearson Chi-Square test was used. Time-to-event variables were summarized using the Kaplan-Meier analysis.

The sample size calculation used prior data for etanercept in an adult psoriasis population where the PASI 75 response rates at Week 12 were 30% for etanercept and 10% for placebo. A sample size of 100 subjects per treatment group was calculated to have 93% power to detect a difference of at least 20% between the etanercept dosing regimen and placebo for the primary efficacy endpoint using a 2 sided Fisher's exact test at a significance level of 0.05.

### ***Results***

A total of 211 subjects were randomised to treatment: 106 to etanercept and 105 to placebo. There were 108 (51.2%) males, 103 (48.8%) females and the age range was 4 to 17 years. The treatment groups were similar in demographic and baseline characteristics. Subject disposition was complex. A total of 100 subjects in the etanercept group and 78 in the placebo completed the 12 week double blind treatment phase. There were five subjects in the etanercept group and 27 in the placebo that entered the escape arm. Two subjects from the placebo group and one from the etanercept withdrew from the study. Hence, 208 subjects entered the 24 week open label phase. Of these subjects, 138 were randomised in the 12 week withdrawal phase: 68 to etanercept and 69 to placebo.

For the primary efficacy outcome measure etanercept was superior to placebo; PASI 75 response at Week 12 was achieved by 60 (57%) subjects in the etanercept group and 12 (11%) in the placebo group ( $p < 0.0001$ ) (Table 2).

**Table 2. PASI Responses During Double-blind Period (ITT Subset With Treatment Failure Imputation) Subjects Who Entered the Escape Arm Considered Treatment Failures at Time of Entering Escape Arm**

		Placebo	Etanercept 0.8 mg/kg QW	p-value <sup>a</sup>
≥ 50	Week 2	6/105 ( 6%)	9/106 ( 8%)	0.4323
	Week 4	12/105 ( 11%)	50/106 ( 47%)	<0.0001
	Week 8	20/105 ( 19%)	75/106 ( 71%)	<0.0001
	Week 12	24/105 ( 23%)	79/106 ( 75%)	<0.0001 <sup>b</sup>
≥ 75	Week 2	1/105 ( 1%)	1/106 ( 1%)	1.0000
	Week 4	3/105 ( 3%)	10/106 ( 9%)	0.0466
	Week 8	5/105 ( 5%)	47/106 ( 44%)	<0.0001
	Week 12	12/105 ( 11%)	60/106 ( 57%)	<0.0001 <sup>b</sup>
≥ 90	Week 2	0/105 ( 0%)	0/106 ( 0%)	N/A
	Week 4	1/105 ( 1%)	3/106 ( 3%)	0.3184
	Week 8	2/105 ( 2%)	14/106 ( 13%)	0.0019
	Week 12	7/105 ( 7%)	29/106 ( 27%)	<0.0001 <sup>b</sup>

Treatment groups represent original randomized treatment

<sup>a</sup> Two-sided Cochran-Mantel-Haenszel test stratified by age group

<sup>b</sup> Nominal p-value - Overall significance level for primary and secondary endpoints at week 12 was controlled at 0.05 using a sequential testing scheme in the following order: PASI 75 response, PASI 50 response, clear/almost clear status of sPGA, percent improvement from baseline in CDLQI, and PASI 90 response.

Efficacy was demonstrated for both the 4 to 11 year age group and the 12 to 17 year age group. In the 4 to 11 year age group, a PASI 75 response at Week 12 was achieved by 22 ( 58%) of the etanercept group and 10 ( 26%) of the placebo,  $p=0.0053$ . In the 12 to 17 year age group, a PASI 75 response at Week 12 was achieved by 38 ( 56%) of the etanercept group and 11 (16%) of the placebo,  $p=0.0001$ . Response was not influenced by race, sex, geographical region, previous use of systemic or photo therapies or baseline body mass index. The secondary efficacy outcome measures also supported efficacy. There were 79 (75%) subjects in the etanercept group and 24 (23%) in the placebo ( $p<0.0001$ ) who achieved a PASI 50 response at Week 12 (Table 2). Clear/almost clear status of sPGA at Week 12 was achieved by 56 (53%) subjects in the etanercept group and 14 (13%) subjects in the placebo,  $p<0.0001$ . The mean (standard error of the mean (SE)) percent improvement from baseline in CDLQI at Week 12 was 52.3 (6.1) for the etanercept group and 17.5 (8.3) for the placebo group,  $p<0.0001$  (Table 3). There were 29 (27%) subjects in the etanercept group and seven (7%) in the placebo group ( $p<0.0001$ ) who achieved a PASI 90 response at Week 12 (Table 2).

**Table 3. Mean (SE) Percent Improvement From Baseline in Total Score on CDLQI During Double blind Period (ITT Subset With Treatment Failure Imputation) Subjects Who Entered the Escape Arm Considered Treatment Failures at Time of Entering Escape Arm**

		Placebo	Etanercept 0.8 mg/kg QW	p-value <sup>a</sup>
Week 2	Mean (SE)	8.0 (7.3)	27.4 (4.9)	0.0333
	SD	73.7	48.7	
	Median	15.5	33.3	
	Min, Max	-300.0, 100.0	-200.0, 100.0	
	n	102	100	
Week 4	Mean (SE)	11.0 (12.7)	34.5 (7.5)	0.0046
	SD	127.9	74.9	
	Median	33.3	50.0	
	Min, Max	-1000.0, 100.0	-400.0, 100.0	
	n	102	100	
Week 12	Mean (SE)	17.5 (8.3)	52.3 (6.1)	<0.0001 <sup>b</sup>
	SD	84.1	61.0	
	Median	15.5	66.7	
	Min, Max	-600.0, 100.0	-400.0, 100.0	
	n	102	100	

Treatment groups represent original randomized treatment

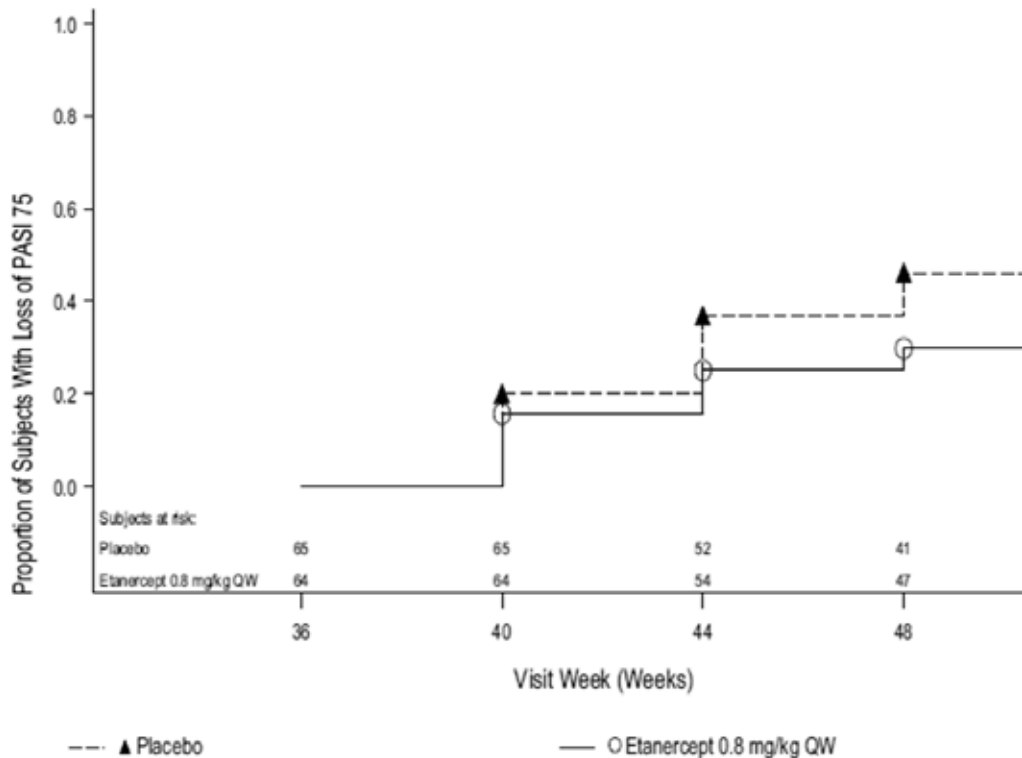
CDLQI age stratification: 4-12 years old versus 13-17 years old

<sup>a</sup> Two-sided van Elteren's test stratified by age group

<sup>b</sup> Nominal p-value - Overall significance level for primary and secondary endpoints at week 12 will be controlled at 0.05 using a sequential testing scheme in the following order: PASI 75 response, PASI 50 response, clear/almost clear status of sPGA, percent improvement from baseline in CDLQI, and PASI 90 response.

PASI responses were maintained through the 24 week open label phase at around 86 to 90% for PASI 50, 65 to 69% for PASI 75 and 34 to 41% for PASI 90. There was little difference between the treatment groups in the PASI response during the withdrawal phase. However, during the withdrawal phase a loss of PASI 75 response was more common in the placebo group than the etanercept (Figure 1). No subject had rebound of disease during the withdrawal period. For subjects who achieved a PASI 75 response and were randomised at Week 36 into the double blind withdrawal phase, the etanercept group maintained a significantly greater response rate at Week 48: PASI 50 for 53 (83%) subjects in the etanercept group and 39 (60%) subjects in the placebo group ( $p=0.0061$ ); PASI 75 for 46 (72%) subjects in the etanercept group and 34 (52%) subjects in the placebo group ( $p=0.0294$ ); and PASI 90 for 34 (53%) subjects in the etanercept group and 22 (34%) subjects in the placebo group ( $p=0.0335$ ).

**Figure 1. Time to Loss of PASI 75 Response for PASI 75 Responders Who Entered the Randomized Withdrawal Period.**



There were insufficient numbers of subjects with joint pain and therefore no significant difference between the treatment groups. The 12 week treatment period was of insufficient duration to detect any effect on growth parameters. There was no significant difference between the groups in the photograph derived NAPS I score. There was no significant difference between the treatment groups in the Stein Impact on Family scale, the Peds QL scores or the Harter's Self-perception Profile for Children/Adolescents.

In a post hoc subgroup analysis there were comparable efficacy results in the 6 to 7 year age group for PASI but there were insufficient subjects to support hypothesis testing. Response was maintained during the open label phase.

### Supportive Efficacy Data

#### Study 20050111

Study 20050111 was a multicentre, open label extension of Study 20030211. The study was conducted at 37 sites in the US and Canada. The study included subjects 4 to 17 years old with moderate to severe plaque psoriasis who had completed Study 20030211 or received substantial benefit (achieved a minimum of PASI 50) from etanercept on or after Week 12, and did not have a serious AE (SAE) or other clinically significant adverse event considered related to the investigational product. The subjects received etanercept 0.8 mg/kg (up to an intended dose of 50 mg) once weekly by subcutaneous injection. The study was planned to have a total duration of 264 weeks but the submitted report covered the first 96 weeks of the planned total duration. The efficacy outcome measures were: PASI 50, PASI 75, PASI 90, sPGA and CDLQI. The safety outcome measures were: AEs, infectious episodes, injection site reactions and laboratory tests.

The study included 182 subjects: 92 (50.5%) males, 90 (49.5%) females, with an age range of 4 to 17 years. There were 63 (34.6%) subjects aged 4 to 11 years and 119 (65.4%) aged 12 to 17 years. Baseline disease severity is summarised in Table 4.

**Table 4. Baseline Disease Summary (Based on Study 20050111 Baseline)**

	Study 20030211 Placebo (N = 92)	Study 20030211 Etanercept 0.8 mg/kg QW (N = 90)	All (N = 182)
<b>Psoriasis BSA (%)</b>			
n	91	89	180
Mean	7.98	6.36	7.18
SD	12.16	7.69	10.20
Min, Max	0.0, 68.0	0.0, 37.0	0.0, 68.0
<b>Psoriasis Area and Severity Index</b>			
n	91	89	180
Mean	5.27	4.39	4.84
SD	5.66	3.82	4.84
Min, Max	0.0, 26.9	0.0, 18.6	0.0, 26.9
<b>Static Physician Global Assessment of Psoriasis</b>			
Unknown	1 (1.1)	1 (1.1)	2 (1.1)
0	7 (7.6)	9 (10.0)	16 (8.8)
1	37 (40.2)	28 (31.1)	65 (35.7)
2	30 (32.6)	39 (43.3)	69 (37.9)
3	15 (16.3)	12 (13.3)	27 (14.8)
4	2 (2.2)	1 (1.1)	3 (1.6)
5	0 (0.0)	0 (0.0)	0 (0.0)
<b>Total Children's Dermatology Life Quality Index</b>			
n	88	84	172
Mean	2.26	2.89	2.57
SD	3.06	3.50	3.29
Min, Max	0.0, 15.0	0.0, 17.0	0.0, 17.0
<b>Total Harter's Self-Perception Profile for Children</b>			
n	38	29	67
Mean	3.13	3.08	3.11
SD	0.54	0.46	0.50
Min, Max	2.3, 4.0	2.4, 3.9	2.3, 4.0

**Table 4. (cont)**

	Study 20030211 Placebo (N = 92)	Study 20030211 Etanercept 0.8 mg/kg QW (N = 90)	All (N = 182)
<b>Total Harter's Self-Perception Profile for Adolescents</b>			
n	45	52	97
Mean	3.08	2.97	3.02
SD	0.44	0.45	0.45
Min, Max	2.3, 3.9	1.9, 3.8	1.9, 3.9
<b>Patient Assessment of Joint Pain</b>			
n	23	13	36
Mean	1.96	1.62	1.83
SD	2.51	2.26	2.40
Min, Max	0.0, 8.0	0.0, 7.0	0.0, 8.0

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Treatment groups represent original randomized treatment from Study 20030211  
N = Number of subjects who were enrolled

A total of 140 (78.9%) subjects completed 96 weeks of treatment. Three (1.6%) subjects were withdrawn from the study due to an AE. Mean PASI 50 was achieved by 87% to 92% of subjects through the 96 week treatment period. PASI 75 was achieved by 55% to 68% of subjects and PASI 90 was achieved by 30% to 37% of subjects. There was no significant change in the distribution of sPGA scores. There was no significant change in CDLQI scores throughout the 96 week treatment period. There were relatively few subjects with joint pain (41) and no significant change in joint pain score from baseline (mean (standard deviation (SD)) 1.8 (0.4)) to Week 96 (0.7 (0.3)). There was no significant change in Harter's self perception profile. Mean (SE) body mass index (BMI) percentile decreased from 80.77 (1.78) at baseline to 70.65 (2.88) at Week 96. Mean (SE) height standard deviation score was 0.21 at baseline and 0.29 (0.10) at Week 96.

A response was also maintained through to Week 96 in the 6 to 7 year old subgroup.

### **Evaluator's Overall Conclusions on Clinical Efficacy**

Efficacy has been demonstrated for etanercept (Enbrel) in subjects with moderate to severe plaque psoriasis aged 4 to 17 years. Efficacy was demonstrated in comparison with placebo. The response was clinically significant. The response was maintained for 96 weeks. There was no apparent rebound effect on ceasing treatment. Efficacy was demonstrated separately for the 4 to 11 year age group and the 12 to 17 year age group. Efficacy was apparent for the 6 to 7 year age group.

### **Safety**

Safety data were provided from both studies evaluated for efficacy (Studies 20030211 and 20050111).

### **Patient Exposure**

In Study 20030211 during the double blind treatment phase, 106 subjects received a median (range) of 24 (1 to 26) doses. During the open label phase, 208 subjects received a median (range) of 48 (4 to 72) doses. During the double blind withdrawal phase, 68 subjects received a median (range) of 22 (4 to 26) doses. During the retreatment phase, 13 subjects received a median (range) of ten (8 to 20) doses. There were 19 subjects aged <8 years, nine of whom were aged <6 years.

In Study 20050111, a total of 181 subjects received a median (range) of 182 (14 to 192) doses. Duration of exposure was for a median (range) of 1000 (300 to 1396) days. There were 14 subjects aged <8 years, three of whom were aged <6 years.

### **Adverse Events**

In Study 20030211 the overall rates of treatment emergent AEs (TEAEs) and infections were similar in the etanercept and placebo group. For etanercept the incidence of events was 554.8/100 patient years exposure and for placebo the rate was 685.3/100 patient years exposure. The most commonly reported events in both treatment groups were upper respiratory tract infection, headache and nasopharyngitis. Events reported more commonly in the etanercept group were: streptococcal pharyngitis, gastroenteritis and arthralgia, which occurred at exposure adjusted rates of 14.3, 9.8 and 8.5 events per 100 subject years, respectively, in the etanercept group. This can be compared with 3.3, 0 and 0 events per 100 subject years, respectively, in the placebo group. There were no clinically significant changes in vital signs reported.

In Study 20050111, the most frequently reported TEAEs were: upper respiratory tract infection in 45 (24.9%) subjects, nasopharyngitis in 31 (17.1%) subjects, streptococcal pharyngitis in 23 (12.2%) subjects and headache in 21 (11.6%) subjects.

In Study 20030211, injection site reactions from etanercept were reported in seven (6.6%) subjects: pain in two (1.9%) subjects, reaction in two (1.9%) subjects, anaesthesia in one (0.9%) subjects, bruising in one (0.9%) subject and pruritis in one (0.9%) subject. In Study 20050111, injection site reactions from etanercept were reported by ten (5.5%) subjects: erythema in five (2.8%) subjects, reaction in three (1.7%) subjects, irritation in one (0.6%) subject and pruritis in one (0.6%) subject.

### **Serious Adverse Events and Deaths**

In Study 20030211 there were four serious AEs (SAEs)/infections reported in three subjects, all of which occurred during the open label phase: benign ovarian mass and pneumonia during treatment with etanercept and dehydration/gastroenteritis during placebo treatment.

In Study 20050111 there were five SAEs reported in three (1.7%) etanercept subjects: anxiety, postoperative intestinal obstruction and dehydration/abdominal pain/abortion.

In Study 20030211 and Study 20050111 there were no deaths reported.

### **Laboratory Findings**

In Study 20030211 there were no clinically significant laboratory abnormalities.

In Study 20050111, one subject was reported with a haemoglobin level of 72 g/L, one with a platelet count of  $34 \times 10^9$ /L, one with a creatinine concentration of 477 mmol/L and one with an ALT level of 253 U/L. All of these abnormalities resolved during the study.

### **Safety in Special Populations**

During the double blind phase of Study 20030211, five (45.5%) subjects aged 6 to 7 years in the etanercept group and five (83.3%) subjects in the placebo were reported with TEAEs. During the open label phase TEAEs occurred at the rate of 491.32/100 patient years exposure. There was no obvious pattern to the TEAEs. During Study 20050111, TEAEs occurred at the rate of 113.9/100 patient years exposure. No non infectious SAEs were reported in this population in either study. There were no clinically significant laboratory abnormalities reported in this age group.

During the double blind phase of Study 20030211, four (36.4%) subjects aged 6 to 7 years in the etanercept group and one (16.7%) subject in the placebo were reported with



infections. During the open label phase, infections occurred at the rate of 275.14/100 patient years exposure. These were predominantly upper respiratory tract infections. During Study 20050111, infections occurred at the rate of 58.7/100 patient years exposure. There was one serious infection reported during the open label phase of Study 20030211: a 7 year old female subject experienced lobar pneumonia and was withdrawn from the study.

### **Immunological Events**

In Study 20030211, twenty (10%) of subjects developed antibodies to etanercept but none of these were described as neutralising antibodies.

### **Safety Related to Drug-Drug Interactions and Other Interactions**

No data were provided regarding drug-drug interactions.

### **Discontinuation Due To Adverse Events**

In Study 20030211, six subjects withdrew from the study due to an adverse event or infection: one subject during the double blind phase (acute bronchospasm) and five subjects during the open label phase (progression of psoriasis, skin infection, atopic dermatitis, left lower lobe pneumonia, and muscle cramps).

In Study 20050111, two (1.1%) subjects withdrew because of AEs: one subject due to Crohn's disease and one subject due to sinusitis.

### **Post Marketing Experience**

No postmarketing data were included in the submission.

### **Evaluator's Overall Conclusions on Clinical Safety**

The AE profile is similar in incidence and pattern to that expected for the population of subjects included in the studies. The pattern of infections was also similar to that expected for the target population. The rates of AEs in the etanercept group were similar to those of the placebo group. There were few SAEs and no deaths reported during the studies.

### **Clinical Summary and Conclusions**

The sponsor has conducted a development program with the intention of demonstrating efficacy and safety for etanercept for paediatric patients aged 4 to 17 years with moderate to severe plaque psoriasis. Etanercept is currently approved for the treatment of 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. The sponsor is applying for the new indication in children 6 years and over but not for the 4 year and 5 year age groups. This appears to be because of safety concerns expressed by other regulatory agencies. These concerns relate to general concerns about the long term safety of biological entities that block the action of TNF- $\alpha$  and to the relative paucity of data in children aged less than 8 years for the requested indication.

### **Benefit Risk Assessment**

#### ***Benefits***

Efficacy has been demonstrated for etanercept (Enbrel) in subjects with moderate to severe plaque psoriasis aged 4 to 17 years. Efficacy was demonstrated in comparison with placebo. The response was clinically significant. The response was maintained for 96 weeks. There was no apparent rebound effect on ceasing treatment. Efficacy was demonstrated separately for the 4 to 11 year age group and the 12 to 17 year age group. Efficacy was apparent for the 6 to 7 year age group.

**Risks**

The AE profile is similar in incidence and pattern to that expected for the population of subjects included in the studies. The pattern of infections was also similar to that expected for the target population. The rates of AEs were similar in the etanercept group and the placebo group. There were few SAEs and no deaths reported during the studies.

**Safety Specification**

The data presented in the submission did not indicate any additional identified or potential risks.

**Balance**

The risk benefit profile is favourable for Enbrel (etanercept) for the indication of:

*Treatment of chronic, moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or photo therapies.*

**Conclusions and Proposed Conditions for Registration**

It was recommended that the application for extending the indications of for Enbrel (etanercept) should be approved as per indication described above.

The sponsor should continue active surveillance of the paediatric population treated with Enbrel (etanercept) for serious infections and for the development of long term adverse events such as lymphoma and other malignancies.

## **V. Pharmacovigilance Findings**

**Risk Management Plan**

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

**Safety Specification (SS)**

The sponsor provided a summary of Ongoing Safety Concerns which are shown at Table 5.

**Table 5. Ongoing Safety Concerns**

Important identified risks – all indications	Serious infection Lupus-like reactions Injection site reactions Allergic reactions Central demyelinating disorders Aplastic anemia and pancytopenia
Important identified risks - specific indications	Change in morphology and/or severity of Psoriasis (adults and pediatric)
Important potential risks – all indications	Malignancy Sarcoid/granuloma AI Renal Disease Amyotrophic lateral sclerosis Myasthenia gravis Peripheral demyelinating events (Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) and Guillain-Barre Syndrome (GBS)) Encephalitis/leukoencephalomyelitis Liver events in patients with history of hepatitis Liver failure Hepatic cirrhosis and fibrosis Adverse pregnancy outcomes Potential for Medication Error (Pre-filled pen) Male infertility Weight Gain
Important potential risks - specific indications	Growth and development (JIA and Pediatric psoriasis) Acute ischemic CV events (all adult indications) CHF (all adult indications) Inflammatory Bowel Disease - JIA
Important missing information	Use in hepatic and renal impaired patients Use in different ethnic origins Use in pregnant women

**OPR evaluator comment**

Pursuant to the evaluation of the clinical aspects of the safety specification (SS), the above summary of the Ongoing Safety Concerns is considered acceptable.

Nevertheless this report only assesses those aspects of the RMP relating to the specific extension of indications (that is, paediatric plaque psoriasis). Therefore the following important potential risks will not be reviewed:

- Acute ischemic cerebral vascular (CV) events
- Chronic heart failure (CHF)
- Inflammatory Bowel Disease

In this context the sponsor has stated that the newly identified potential risks included during the 2010 update of the Etanercept 'All Indication' RMP are as follows:

- *Weight gain*: results of recently published studies found statistically significant increases in body weight and BMI in patients who received anti-TNF therapies for RA, psoriasis, and spondyloarthritis. The sponsor reports that many factors can contribute to weight gain and study designs varied considerably, therefore the results of these independent studies were difficult to interpret.; and
- *Male infertility*: a concern was raised based on an observation of clinical data that suggested anti TNF alpha therapy may decrease sperm motility and affect morphology.

The sponsor states that inhibiting TNF alpha during testis maturation may affect spermatogenesis and potentially fertility.

### Pharmacovigilance Plan

The sponsor proposes routine pharmacovigilance activities, consistent with the activities outlined in *3.1.2 Routine pharmacovigilance practices, Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)*, to monitor all the specified Ongoing Safety Concerns pertaining to the extension of indications.

In addition, the sponsor proposes to further monitor all the specified Ongoing Safety Concerns pertaining to the extension of indications, except for the important potential risks: 'Potential for medication error (Pre filled pen)', 'Male infertility' and 'Weight Gain' and the important missing information: 'Use in hepatic and renal impaired patients', by conducting Study 20050111. The sponsor proposes to further monitor the important identified risk: 'Serious infection' and the important potential risk: 'Malignancy' via the ongoing Study 0881X1-4654.

Furthermore the sponsor reports that Events of Special Circumstance (ESC) will have additional data collected using an Events specific questionnaire. The Ongoing Safety Concerns involved in this additional pharmacovigilance activity are

- Important Identified Risks:  
'Central demyelinating disorders' and 'Aplastic anaemia and pancytopenia',
- Important Potential Risks:  
'Malignancy', 'Autoimmune (AI) Renal disease', 'Myasthenia gravis', 'Peripheral demyelinating events (CIDP and GBS)', 'Liver events in patients with history of hepatitis', 'Liver failure', 'Hepatic cirrhosis and fibrosis' & 'Adverse pregnancy outcomes' and
- Important Missing Information:  
'Use in pregnant women'.

### Risk Minimisation Activities

The sponsor has concluded and provided justification that routine risk minimisation activities for all the specified Ongoing Safety Concerns pertaining to the extension of indications are sufficient, except:

- for the Important Potential Risks: 'Autoimmune (AI) Renal disease', 'Amyotrophic lateral sclerosis', 'Myasthenia gravis', 'Peripheral demyelinating events (CIDP and GBS)', 'Encephalitis/leukoencephalomyelitis', 'Liver failure', 'Hepatic cirrhosis and fibrosis', 'Male Infertility', 'Weight Gain' & 'Growth and development' and the Important Missing Information: 'Use in different ethnic origins', as there are currently insufficient information to assess; and
- for the Important Identified Risk: 'Serious infection' and the important potential risk: 'Potential for medication error (Pre filled pen)', for which additional risk minimisation activities have also been proposed. To inform patients (or parents) to monitor for the risk of infections the sponsor has proposed patient alert cards be provided to etanercept prescribing physicians for distribution to patients receiving etanercept. In regard to the important potential risk: 'Potential for medication error (Pre filled pen)', the sponsor has stated that clear Package Leaflet Instructions for use of the Pre filled pen will be provided with this product. In preparation for the introduction of Pre filled Pen (PFP), the sponsor has also developed a comprehensive plan to train and educate patients and health care professionals (HCPs) on the proper use of the PFP.

The sponsor states that numerous resources have been developed to support efforts to train patients, care givers and HCPs in the appropriate use of the PFP. Many of these resources were based on resources developed and utilised to train patients in the US, where a similar Enbrel PFP has been utilised for more than two years prior to the launch of the Enbrel PFP in the EU. Based on the experience from the US, EU post launch experience and market research studies, numerous enhancements have been made to the HCP and patient training materials and resources including:

The sponsor states that Pfizer staff has been trained on the correct use of the PFP in order to facilitate proper training techniques. Appropriate healthcare professionals (HCPs; physicians and nurses) are then trained by Pfizer personnel post PFP approval, but prior to PFP availability. A comprehensive plan is in place to ensure that Pfizer personnel are certified to effectively train HCPs. Furthermore, training materials and PFP demonstration kits are available to support patient and caregiver training.

### Summary of Recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application and is applicable without modification in Australia unless so qualified:

- If this application is approved the following specific condition of registration should be applied: *“The Risk Management Plan Version: 2.0, dated 31 March 2011, to be revised as specified in the sponsor’s correspondence dated 30 August 2011, must be implemented.”*
- In principle there was no objection to the sponsor implementing additional pharmacovigilance activities to further monitor the specified Ongoing Safety Concerns. However, the ongoing studies are not considered to be part of the planned clinical studies in the pharmacovigilance plan. Therefore the related study protocols have not been reviewed. Nevertheless an update on the progress/results/analysis of this study, as outlined in the RMP, will be expected in future PSURs.
- In regard to the ESC questionnaires the sponsor should be aware that changes to tables of the current RMP will be required in the next version of the RMP to reflect the monitoring of the important identified risk: ‘Aplastic anaemia and pancytopenia’ and the important potential risks: ‘Autoimmune (AI) Renal disease’, ‘Myasthenia gravis’, ‘Liver events in patients with history of hepatitis’, ‘Liver failure’ and ‘Hepatic cirrhosis and fibrosis’ via routine pharmacovigilance only.
- The sponsor should indicate when the next version of the RMP is expected to be available.
- The table describing ‘Safety Concerns and Additional Pharmacovigilance Actions’ appears to be inconsistent with the table of ‘Summary of the EU Risk Management Plan’; specifically the inclusion of Study 20050111 as an additional pharmacovigilance activity for the important potential risk: ‘Autoimmune (AI) Renal disease’. This apparent internal inconsistency should be corrected in the next version of the RMP.
- The Ongoing Safety Concerns, other than the Important Identified Risk: ‘Serious infection’ and the important potential risk: ‘Potential for medication error (Pre filled pen)’, would not appear to warrant additional risk minimisation activities. Therefore the sponsor’s conclusion that routine risk minimisation activities for all the specified Ongoing Safety concerns pertaining to the extension of indications are sufficient was considered acceptable.
- The sponsor’s proposed Risk Minimisation Plan (RiMP) would appear to be reasonable. However, the sponsor should provide an assurance that final copies of the training program and of the educational materials, together with evidence of their readability and understanding of the key points by the target Australian audience, will be

submitted to the TGA prior to being used and distributed in Australia. <sup>3</sup> The sponsor should provide an assurance that an anticipated schedule of conducting the market research in Australia within the first three years post-approval of the proposed indication to assess the effectiveness of educational materials and training programs developed to support HCPs treating patients with paediatric psoriasis, the patients themselves and their carers will be submitted to the TGA once available<sup>4</sup>. The sponsor states that this research will be repeated on a periodic basis should it be justified by signals uncovered during routine pharmacovigilance monitoring. It was suggested that such periodic assessment should be rather based upon whether additional risk minimisation activities are still considered necessary and therefore continue to be implemented. The sponsor should provide an assurance that this part of the RMP will be amended accordingly.

## VI. Overall Conclusion and Risk/Benefit Assessment

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

### Quality

There was no requirement for a quality evaluation in a submission of this type.

### Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

### Clinical

The clinical evaluator has recommended approval of the application. The TGA has adopted a European Union (EU) guideline on clinical data requirements for medicines used in the treatment of psoriasis<sup>5</sup>.

Evidence to support the new indication comes from one pivotal randomised, double blind, placebo controlled trial (Study 2003-0211) and one follow on open extension study (Study 2005-0111). The pivotal study has been published<sup>6</sup>.

### Pharmacokinetics (PK)

Trough plasma levels were measured in subjects receiving etanercept at the proposed dose of 0.8 mg/kg once weekly in the pivotal study. At steady state mean trough levels ranged from  $1.6 \pm 0.8$  to  $2.1 \pm 1.2$  mg/L. Previously evaluated data suggested that the trough level for adult psoriasis patients receiving 50 mg once weekly was  $1.5 \pm 1.0$  mg/L. Systemic exposure may therefore be greater in paediatric patients.

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<sup>3</sup> In response to this request, the sponsor indicated that it would provide final copies of the paediatric psoriasis-specific educational materials once Pharmaceutical benefits Scheme (PBS) listing is obtained and the proposed materials have been developed.

<sup>4</sup> In response, the Sponsor explained that it does not expect any clinical use in paediatric psoriasis, prior to reimbursement, and hence intends to conduct the research within 3 years post-reimbursement, instead of within 3 years post-approval.

<sup>5</sup> CHMP/EWP/2454/02. Guideline of the clinical investigation of medicinal products indicated for the treatment of psoriasis. <http://www.tga.gov.au/pdf/euguide/ewp245402en.pdf>

<sup>6</sup>Paller AM *et al* (2008). Etanercept treatment for children and adolescents with plaque psoriasis. 358: 241-251.

**Efficacy**

The pivotal study (2003-0211) enrolled subjects aged 4 to 17 years with a diagnosis of moderate to severe chronic plaque psoriasis characterised by:

- A Psoriasis Area and Severity Index (PASI) score of  $\geq 12$ ;
- A Static Physician's Global Assessment of Psoriasis (sPGA) score of  $\geq 3$ ;
- Involvement of  $\geq 10\%$  of body surface area.

These criteria are consistent with the definition of moderate to severe psoriasis as per the EU guideline<sup>5</sup>.

The study enrolled a total of 211 subjects with a mean age of 12.7 years (range 4 – 17) and a median PASI score of 16.4 (range 12.0 – 56.7). Only 57% of patients had been previously treated with systemic therapies or phototherapy.

The study comprised three phases:

- An initial 12 week randomised (1:1) double blind parallel group comparison against placebo;
- A 24 week open-label phase in which all subjects received etanercept;
- A subsequent 12 week randomised (1:1) double blind parallel group comparison of continued treatment versus withdrawal of treatment.

For the initial double blind phase (Weeks 1-12), the primary endpoint was the percentage of patients who achieved a 75% reduction in their PASI score at 12 weeks. This endpoint has previously been accepted by the Advisory Committee on Prescription Medicines (ACPM) and the TGA for other agents for the treatment of psoriasis and is consistent with the recommendations of the EU guideline<sup>5</sup>. The proportion of patients who achieved a 75% reduction in PASI score was significantly increased in the etanercept arm (57% versus 11%;  $p < 0.0001$ ).

Etanercept treatment was also associated with significant benefit on secondary efficacy endpoints (PASI 50, PASI 90, sPGA and Children's Dermatology Life Quality Index).

In the open label phase (Weeks 13-36), those subjects who had previously received placebo responded to etanercept therapy with 65% achieving a PASI 75. Efficacy was maintained out to 36 weeks in those subjects previously treated with etanercept.

In the withdrawal phase (Weeks 37-48), all subjects who had achieved a PASI 75 response were again randomised to continued treatment or to withdrawal (placebo). Subjects randomised to withdrawal had an increased incidence of loss of PASI 75 response.

Study 2005-0111 was an open label extension of the pivotal study. Subjects were treated with the same dose (0.8 mg/kg, up to 50 mg, weekly). Data presented were for an additional 96 weeks of treatment. The proportion of patients with a PASI 75 response was maintained out to 96 weeks.

**Safety**

A total of 210 subjects were treated with etanercept in the submitted studies. There were no marked differences between etanercept and placebo in the incidence of adverse events. Etanercept treatment was associated with an increased incidence of streptococcal pharyngitis, gastroenteritis and arthralgia. No new safety issues were identified by the evaluator from the submitted studies.

## Risk Management Plan

The Risk Management Plan submitted by the sponsor has been found to be acceptable by the TGA's Office of Product Review (OPR).

## Risk-Benefit Analysis

### Delegate Considerations

#### 1. *Safety concerns (regarding malignancies) raised by the FDA*

In 2008-2009 the FDA conducted a safety review of TNF blockers and the development of lymphoma and other cancers in children and adolescents. The review concluded that there was an increased risk of such malignancies in this population and required sponsors of all products in this class to include warnings in their product literature. Information is available on the FDA website regarding this review<sup>7</sup>. The review was largely based on patients receiving TNF blockers for inflammatory bowel disease or juvenile idiopathic arthritis (JIA).

According to the Australian sponsor, an application for approval of etanercept for paediatric psoriasis had been lodged with the FDA in 2007. It was based on the same pivotal study included in the current Australian application. The FDA indicated it would approve the application only if further studies were conducted, related to this safety review. The US sponsor (Amgen) subsequently withdrew their application. *In the pre-ACPM response, the sponsor is requested to provide further detail on the type of information that had been sought by the FDA.*

An application to the Canadian regulator was also withdrawn after a similar request for further studies.

#### 2. *Assessment of benefits versus risks*

The pivotal study demonstrated efficacy of etanercept in the treatment of paediatric psoriasis and the open extension study indicates that efficacy is maintained over the long term. There were no new safety issues raised by the submitted studies and the safety profile of the drug appears acceptable in the short term. Foreign regulators have raised questions about long term safety, specifically in relation to the development of malignancies and appear to have concluded that the risks have not been adequately defined in the paediatric psoriasis population.

Etanercept is already approved in Australia for use in paediatric patients (aged 4 to 17 years) with JIA, and the current PI includes warnings regarding the possible development of malignancies, including malignancies in children. However, JIA might be considered a more disabling condition than psoriasis and hence the risks of etanercept more likely to be accepted by patients.

It is noteworthy that the FDA's advisory committee, when considering the current application, recommended unanimously that the indication should be restricted to severe psoriasis.<sup>8</sup> The risk-benefit of etanercept may be more favourable in these patients. A similar application has been approved in Europe but also only for patients with severe disease. The European approval also restricts duration of treatment to 24 weeks (with the possibility of repeated courses if required). In Australia the sponsor is seeking approval for patients with moderate to severe disease and is not proposing any limit on the duration of treatment.

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<sup>7</sup><http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm175843.htm>

<sup>8</sup> <http://www.fda.gov/ohrms/dockets/ac/08/minutes/2008-4361m2-Final.pdf>



Psoriasis is a non life threatening and generally non disabling condition and therefore the potential for malignancies is a significant issue, especially as children with psoriasis may have more prolonged exposure to immunosuppressant therapy compared to subjects who develop the condition in adulthood. The Delegate was inclined to reject the application because of the doubts regarding long term safety. An alternative the ACPM may wish to consider is a limited approval in patients with severe disease, with a limit on duration of therapy, as per the European approval.

The Delegate proposed to reject the application due to concerns regarding long term safety. The advice of the Committee was requested.

### **Response from Sponsor**

#### ***Pfizer's Response to the TGA Delegate's Overview and Proposed Action Regarding Licensure of Enbrel for Use in Paediatric Psoriasis***

Pfizer agreed with the Delegate's alternative proposal to limit the indication to patients with severe disease, and to include a limit on duration of therapy, as per the European approval.

Contrary to common belief, psoriasis comprises more than just an inconvenient skin rash. Psoriasis is a chronic, potentially debilitating, systemic, inflammatory disease. It manifests primarily in the skin with patients suffering pruritic and disfiguring skin lesions and a significant percentage developing nail dystrophy and psoriatic arthritis.<sup>9</sup> Patients also have a higher risk of developing significant comorbidities including obesity, diabetes, cardiovascular disease, depression and substance abuse, and have a higher mortality rate than patients without psoriasis.<sup>10</sup> In very rare cases, some types of severe psoriasis can be life threatening or fatal, including in juveniles.<sup>11, 12</sup>

Children with moderate to severe psoriasis have substantially impaired physical, emotional, social, and school functioning compared to healthy children. When compared to children with other serious, chronic childhood diseases, they also fare poorly. Children with moderate to severe psoriasis have greater impairment in quality of life than children with diabetes, and comparable quality of life impairment to children with arthritis (juvenile rheumatoid arthritis, pauciarticular arthritis, polyarticular arthritis, systemic arthritis) and children with asthma<sup>13</sup>. These findings are consistent with those in the adult psoriasis literature, and demonstrate the profound negative multidimensional impact of moderate to severe plaque psoriasis on the daily lives of children and adolescents.

Generally, most cases of psoriasis in juveniles are mild to moderate and respond to topical therapies. For the very small number of children who have treatment resistant, severe disease there are currently no approved systemic therapies, and therefore no effective treatment options available. Such patients are at greatest risk of suffering a reduction in quality of life comparable to, or greater than, children with other serious, systemic illnesses, such as juvenile arthritis. In these patients with severe psoriasis, the risk benefit profile of Enbrel will be more favourable. Given that Enbrel is already approved in Australia for use in paediatric patients with arthritis, use of Enbrel in paediatric patients with psoriasis is appropriate.

The FDA concerns about malignancy with TNF inhibitor use in children and adolescents referred to by the Delegate are noted. An important point to consider is that the majority

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<sup>9</sup>Foley PA, Quirk C, Sullivan JR, *et al.* (2010). *J Eur Acad Dermatol Venereol* 24: 1135-1143

<sup>10</sup>Farley E, Menter A. G (2011). *Ital Dermatol Venereol* 146: 9-15.

<sup>11</sup>Abou-Samra T, Constantin JM, Amarger S. (2004) *Br J Dermatol* 150:353-356.

<sup>12</sup>de Oliveira ST, Maragno L, Arnone M. (2010). *Paediatr Dermatol* 27: 349-354.

<sup>13</sup>Varni JW, Globe DR, Gandra ST, *et al.* *Eur J Pediatr*. DOI 10.1007/s00431-011-1587-2

of malignancies identified by the FDA were in juveniles receiving infliximab or adalimumab for inflammatory bowel disease, who were also receiving concomitant immunosuppressants.<sup>14</sup> The smaller number of malignancies identified in children with juvenile arthritis need to be balanced against any elevated background risk of malignancies, such as lymphoma, in such patients.<sup>15</sup> The differential use of concomitant immunosuppressants and the consequent impact on malignancy risk also needs to be considered. While concomitant immunosuppressants are commonly used with TNF inhibitors in patients with arthritis (and inflammatory bowel disease), such combination therapy is very infrequently employed in patients with psoriasis.

Pfizer Australia believes that a population of patients with severe paediatric psoriasis remains in which the risk/benefit ratio for treatment with Enbrel is favourable. With no other systemic treatments approved for use in this condition, there is a significant unmet medical need in this small group. For these patients who have an impaired level of functioning and quality of life that has been proven to be comparable to other serious, chronic medical disease, such as juvenile arthritis, treatment with Enbrel is an appropriate treatment option.

The sponsor agreed to restrict the proposed indication to

*“... severe plaque psoriasis in children and adolescents from the age of 6 years ...”.*

Pfizer Australia acknowledged the TGA concerns regarding continuous use of Enbrel in paediatric psoriasis and amended the dosing instructions to include a treatment limitation of 24 weeks, consistent with that in the European Summary of Product Characteristics (SmPC) for Enbrel, to read:

*“The recommended dose is 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly for up to 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks. If re-treatment with Enbrel is indicated, the above guidance on treatment duration should be followed.”*

***In relation to safety concerns (re malignancies) raised by the FDA, the Delegate requested the sponsor provide further detail on the type of information that had been sought by the FDA.***

In 2007, Amgen, the US licence holder for Enbrel, submitted the Biologic License Applications (BLA) supplement for the paediatric psoriasis indication. The proposed indication was for the treatment of moderate to severe paediatric psoriasis in children aged 4 to 17 and was based on Study 20030211. On 18 June 2008, the application was considered by the FDA Advisory Committee who agreed that efficacy had been demonstrated for the intended population but was concerned there were insufficient long term data on safety. The Committee voted 8 to 5 in favour to approve the application, however, there was agreement that the indication should be restricted to patients with severe disease.

In July 2008, the FDA stated that the data were inadequate to support approval.

In September 2008 Amgen was advised that the FDA's primary concern was a lack of a detailed plan to address signals of serious risk (infections and malignancy). The reviewer requested additional prospective studies to quantify the risk of serious/opportunistic infections, yet acknowledged that it would require a large study to do so. Regarding malignancy, the reviewer suggested a registry to capture all paediatric patients in the US who are treated with Enbrel for paediatric psoriasis. Again, the reviewer acknowledged

<sup>14</sup> Diak P, Siegel J, La Grenade L *et al.* (2010). *Arthritis Rheum* 62: 2517-2524

<sup>15</sup> Lehman T. (2010). *Arthritis Rheum* 62: 2183-2184

the difficulties associated with this approach considering the frequency of lost-to-follow-up and the fact that health care practitioners might not prescribe Enbrel to a high number of patients. Finally, the reviewer recommended a Risk Evaluation and Mitigation Strategy (REMS) to outline the plan to gather the additional data.

Amgen concluded that it would not be feasible to conduct the additional studies recommended by the FDA. Regarding infections, the number of patients required to detect a doubling of the rate of serious infections in an Enbrel arm over a comparison arm at 80% power with  $\alpha = 0.05$ , would require 1500 total subjects (750 per arm). This estimate was based on a 3 year treatment period, a 20% drop out rate and a rate of 1.2 serious infection events per 100 subject years (the rate of serious infections seen in Study 20030211). Concerning malignancies, Amgen concluded that, due to the limited number of eligible paediatric patients and the rarity of malignancies in children, a prospective registry would not yield meaningful information of risk of malignancy. This was based on the need to collect data over 34,000 subject years to observe a doubling of the background malignancy rate in children and adolescents (based on the background rates from the National Cancer Institute's Surveillance Epidemiology and End Results—SEER).

Subsequently, Amgen formally withdrew the supplemental application in August 2009. It is important to note that the US filing for paediatric psoriasis did not include the 96 week extension study (2005-0111) that was included in the application submitted to the TGA which showed no new safety signals.

#### ***Sponsor's Comment on the Clinical Evaluation Report***

The sponsor wishes to clarify the reason that the 4 year and 5 year age groups are not applied for. There are limited efficacy and safety data in this age group. Only, 9 (4.3%) of the 211 subjects in study 20030211 were 4 or 5 years of age at the baseline of the study. While it is true that the original approval of the paediatric psoriasis indication in the EU was for children and adolescents from the age of 8 years, the EMA Committee for Human Medicinal Products (CHMP) did not identify a specific safety issue associated with younger children. Rather, the CHMP did not feel that the number of subjects in study 20030211 supported approval of this age group.

In addition, as a result of discussions with EMA Pediatric Drug Committee (PDCO) regarding the Enbrel Pediatric Investigational Plan, it became apparent that the relative rarity of paediatric psoriasis and the availability of other anti-psoriatic treatments for patients <6 years of age would represent challenges to the conduct of further clinical investigation in this subset of patients. Consequently, after analyses of the data contributed in the youngest patients in study 20030211 and the long term safety extension study 20050111, the sponsor reached an agreement with EMA that the currently available clinical trial data supported the use of etanercept in children 6 years of age and older. At the same time, EMA waived the need to conduct additional etanercept clinical trials in paediatric psoriasis patients less than 6 years of age. The extended indication to include children ages 6 and 7 received EU Commission approval on 24 August 2011.

#### **Advisory Committee Considerations**

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents advised the following:

**Efficacy**

- The ACPM agreed with the Delegate that the submission demonstrates clinically relevant efficacy and its maintenance over the long term. While the studies included only a limited number of children under the age of 6 years, the ACPM supports use from the age of 4 years as the overall efficacy and safety evidence is favourable in these early onset patients.
- Due to safety concerns, second line systemic therapy, as proposed by the sponsor, is appropriate for this population.

**Safety**

- The ACPM agreed with the Delegate that there were no new safety signals identified in the studies; however, the safety profile depicts only short term use. The malignancy risk and the impact of prolonged exposure to immunosuppressant therapy in this population group were noted.
- To mitigate the safety risks, the ACPM recommended treatment to be limited to chronic, severe plaque psoriasis, for treatment duration of no more than 24 weeks. This would promote adequate vigilance, with treatment ceased after 12 weeks if there is no response.

**Indication**

The ACPM considered this product to have a positive benefit-risk profile for the indication:

*Treatment of chronic, severe plaque psoriasis in children and adolescents from age 4 to 17 years, who are inadequately controlled by, or are intolerant to, other systemic therapies or photo therapies.*

*Duration of therapy to be no longer than 24 weeks and treatment to be ceased after 12 weeks if a significant PASI response is not achieved.*

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided for Enbrel, would support the safe and effective use of this product.

**Outcome**

Based on a review of quality, safety and efficacy, TGA approved the registration of Enbrel containing etanercept *rch* for SC injection, indicated for:

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

Included among specific conditions of registration was that the Risk Management Plan (RMP), version 2.0 dated 31 March 2011, revised as specified in correspondence dated 30 August and 13 October 2011, must be implemented.

**Attachment 1. Product Information**

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at [www.tga.gov.au](http://www.tga.gov.au).

## **Therapeutic Goods Administration**

PO Box 100 Woden ACT 2606 Australia

Email: [info@tga.gov.au](mailto:info@tga.gov.au) Phone: 1800 020 653 Fax: 02 6232 8605

**[www.tga.gov.au](http://www.tga.gov.au)**

Reference/Publication #

# PRODUCT INFORMATION

## ENBREL® Etanercept (rch)

### NAME OF THE MEDICINE

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

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

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

\* not marketed

### DESCRIPTION

Etanercept is a human tumour necrosis factor receptor p75 Fc fusion protein produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian expression system. Etanercept is a dimer of a protein genetically engineered by fusing the extracellular ligand binding domain of human tumour necrosis factor receptor-2 (TNFR2/p75) to the Fc domain of human IgG1. This Fc component contains the hinge, CH<sub>2</sub> and CH<sub>3</sub> regions but not the CH<sub>1</sub> 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 TNF $\alpha$ -mediated growth inhibition of A375 cells. The specific activity of etanercept is 1.7 x 10<sup>6</sup> units/mg.

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

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

### PHARMACOLOGY

#### Pharmacodynamics

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

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

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

## Mechanism of action

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

## Pharmacokinetics

### Absorption

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

### Distribution

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

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

### Excretion

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

Serum concentration profiles at steady state were comparable among patients with RA treated with 50 mg ENBREL powder for injection once weekly and those treated with 25 mg ENBREL powder for injection twice weekly. A single 50 mg/mL injection of ENBREL was also found to be bioequivalent to two simultaneous injections of 25 mg/mL. The mean ( $\pm$  standard deviation) C<sub>max</sub>, C<sub>min</sub> and partial AUC were  $2.4 \pm 1.5$  mg/L,  $1.2 \pm 0.7$  mg/L and  $297 \pm 166$  mg.h/L, respectively, for patients treated with 50 mg ENBREL once weekly (n = 21); and  $2.6 \pm 1.2$  mg/L,  $1.4 \pm 0.7$  mg/L and  $316 \pm 135$  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 ( $\pm$  standard deviation) C<sub>max</sub> and AUC(0-T) are expressed in the table below.

	AUC <sub>0-t</sub> (mg.h/L)	C <sub>max</sub> (mg/L)
1 x 50 mg solution SC (n=33)	535 $\pm$ 192	3.90 $\pm$ 1.49
2 x 25 mg powder SC (n=33)	590 $\pm$ 208	4.09 $\pm$ 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.

#### ***Paediatric patients with plaque psoriasis***

Patients with paediatric plaque psoriasis (aged 4 to 17 years) were administered 0.8 mg/kg (up to a maximum dose of 50 mg per week) of etanercept once weekly for up to 48 weeks. The mean serum steady state trough concentrations ranged from 1.6 to 2.1 mg/L at weeks 12, 24, and 48. These mean concentrations in patients with paediatric plaque psoriasis were similar to the concentrations observed in patients with juvenile idiopathic arthritis (treated with 0.4 mg/kg etanercept twice weekly, up to maximum dose of 50 mg per week). These mean concentrations were similar to those seen in adult patients with plaque psoriasis treated with 25 mg etanercept twice weekly.

### **CLINICAL TRIALS**

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

#### **Adult rheumatoid arthritis**

##### ***Placebo-controlled studies***

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

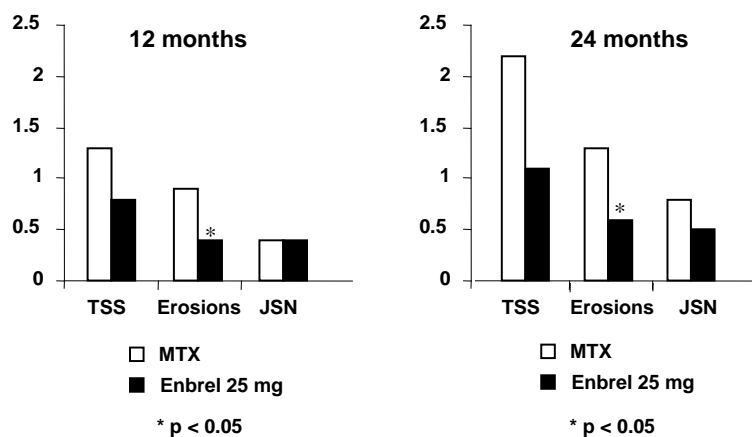
### **Active-Controlled Studies**

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)
<b>ACR 20 Response</b>				
Week 24		73.7%	71.3%	81.8% †,φ
pfpenbra10112		CDS 30.0		5

**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)
Week 52		75.0%	75.8%	84.8% <sup>†,φ</sup>
<b>ACR 50 Response</b>				
Week 24		40.8%	40.4%	59.3% <sup>†,φ</sup>
Week 52		42.5%	48.4%	69.3% <sup>†,φ</sup>
<b>ACR 70 Response</b>				
Week 24		15.4%	17.0%	35.9% <sup>†,φ</sup>
Week 52		18.9%	24.2%	42.9% <sup>†,φ</sup>
<b>DAS<sup>a</sup></b>				
Baseline score		5.5	5.7	5.5
Week 24 score		3.1	3.1	2.5 <sup>†,φ</sup>
Week 52 score		3.0	3.0	2.3 <sup>†,φ</sup>

a: Values for DAS are means.

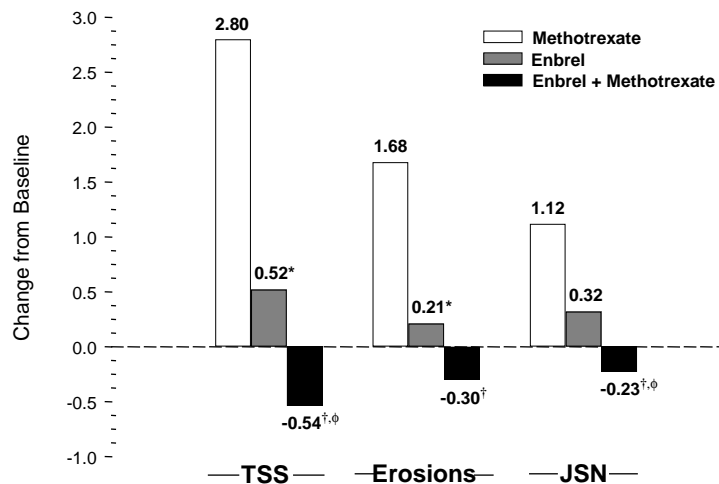
Pairwise comparison p-values: † = p < 0.05 for comparisons of ENBREL + methotrexate vs. methotrexate and φ = p < 0.05 for comparisons of ENBREL + methotrexate vs. ENBREL

The percentage of patients 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  $\phi = p < 0.05$  for comparisons of ENBREL + methotrexate vs. ENBREL

The percentage of patients without progression (TSS change  $\leq 0.5$ ) 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 immunogenicity were assessed in an open label study of etanercept manufactured by the serum-free process (SFP) in patients with rheumatoid arthritis. Based on indirect comparisons with historical data, the results were comparable to two previous phase 3 controlled studies in subjects with RA using etanercept manufactured by a serum-based process.

### Juvenile idiopathic arthritis

The safety and efficacy of ENBREL were assessed in a two-part study of 69 children with polyarticular-course juvenile idiopathic arthritis (JIA) who had a variety of JIA onset types. 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 ( $\leq 0.2$  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  $\geq 30\%$  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  $\geq 30\%$  worsening in three of six JIA core set criteria and a minimum of two active joints. They could also have  $\geq 30\%$  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  $\geq 116$  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 ( $\geq 3$  swollen joints and  $\geq 3$  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  $\geq 2$ cm in diameter. Patients currently on methotrexate therapy (stable for  $\geq 2$  months) could continue at a stable dose of  $\leq 25$ mg/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 <sup>a</sup> (n = 101)
<b>ACR 20</b>	Month 3	15	59 <sup>b</sup>
	Month 6	13	50 <sup>b</sup>
<b>ACR 50</b>	Month 3	4	38 <sup>b</sup>
	Month 6	4	37 <sup>b</sup>
<b>ACR 70</b>	Month 3	0	11 <sup>b</sup>
	Month 6	1	9 <sup>c</sup>
<b>PsARC</b>	Month 3	31	72 <sup>b</sup>
	Month 6	23	70 <sup>b</sup>

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  $\geq 3\%$  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 <sup>a</sup> (n = 66)
<b>PASI 50% improvement</b>	Month 3	15	36 <sup>c</sup>
	Month 6	18	47 <sup>b</sup>
<b>PASI 75% improvement</b>	Month 3	8	12
	Month 6	3	23 <sup>c</sup>

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 ( $\leq 0$  change) in TSS from baseline, compared with subjects in the placebo group.

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

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

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<sup>a</sup>**

	Placebo/ Etanercept (n = 70) <sup>b</sup>	Etanercept (n = 71) <sup>b</sup>
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.

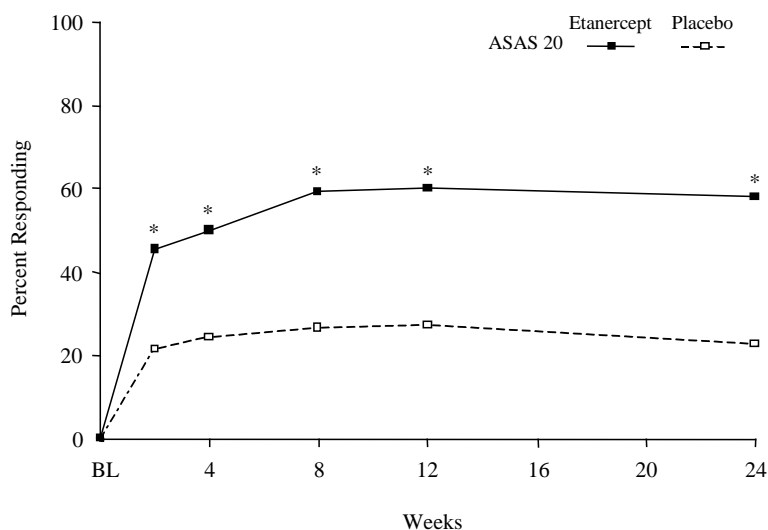
Quality of life in psoriatic arthritis patients was assessed using the Health Assessment Questionnaire (HAQ) and SF-36 instruments. There was a statistically significant improvement in mean HAQ score from 1.1 to 0.5 on a scale of 0 to 3 for patients treated with ENBREL. The SF-36 showed improvements 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  $\geq 30$  for average of duration and intensity of morning stiffness plus VAS scores of  $\geq 30$  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 ( $\leq 10$  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

Mean values at time points	Placebo n = 139		ENBREL <sup>a</sup> n = 138	
	baseline	6 months	baseline	6 months
<b>ASAS response criteria</b>				
Patient global assessment <sup>b</sup>	63	56	63	36
Back pain <sup>c</sup>	62	56	60	34
BASFI <sup>d</sup>	56	55	52	36
Inflammation <sup>e</sup>	64	57	61	33
<b>Acute phase reactants</b>				
CRP (mg/dL) <sup>f</sup>	2.0	1.9	1.9	0.6
<b>Spinal mobility (cm):</b>				
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  $\geq 18$  years old, had active but clinically stable plaque psoriasis involving  $\geq 10\%$  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  $\geq 150\%$  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**

Response	Study 1					Study 2		
	ENBREL					ENBREL		
	Placebo n = 166 wk 12	25 mg BIW n = 162 wk 12	25 mg BIW n = 162 wk 24 <sup>a</sup>	50 mg BIW n = 164 wk 12	50 mg BIW n = 164 wk 24 <sup>a</sup>	Placebo n = 193 wk 12	25 mg BIW n = 196 wk 12	50 mg BIW 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

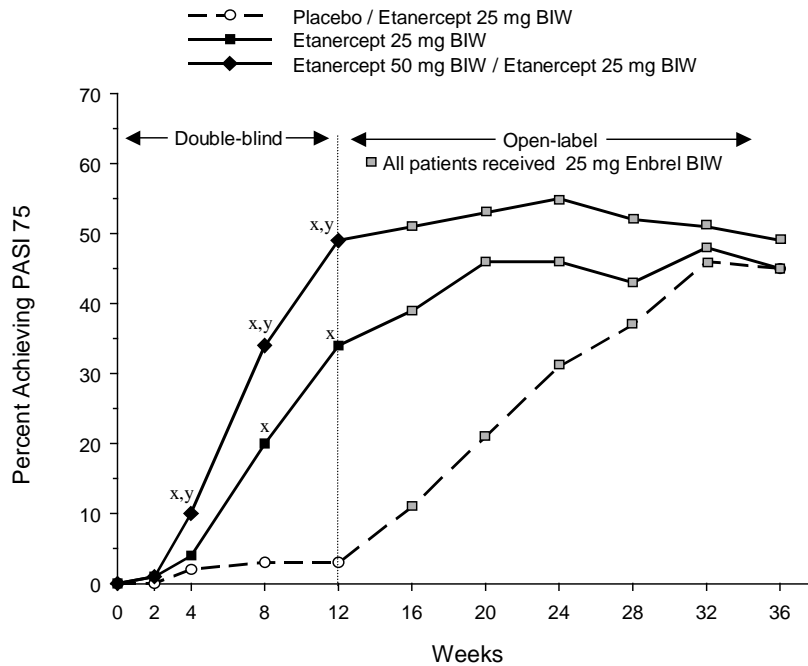
<sup>a</sup> No statistical comparisons to placebo were made at week 24 in Study 1 because the original placebo group began receiving ENBREL 25 mg BIW from week 13 to week 24.

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.

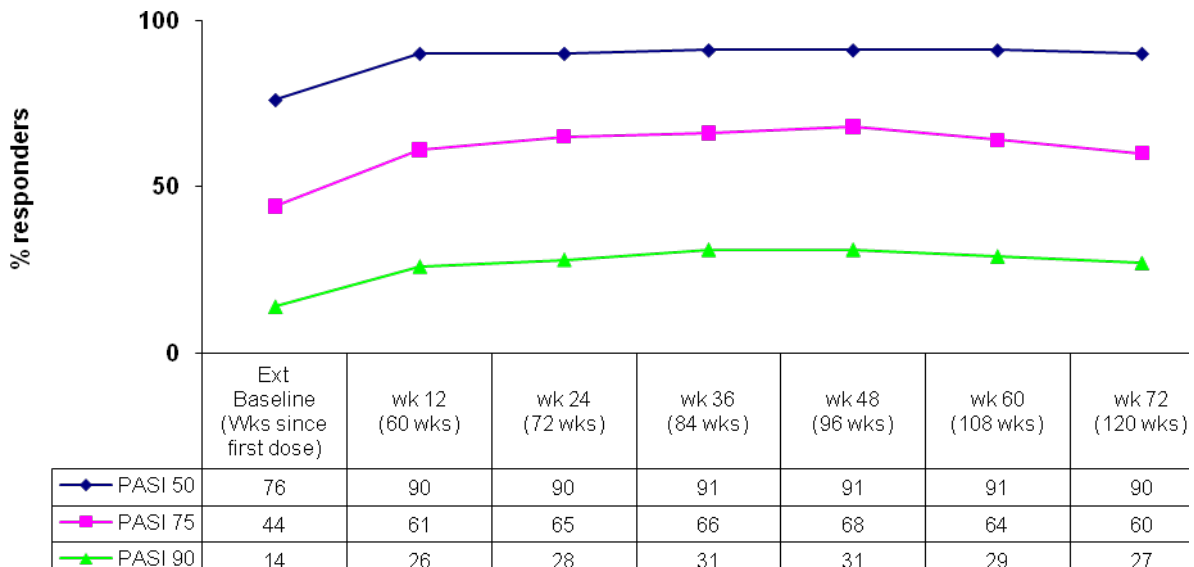
## PASI 75 Response of Patients with Plaque Psoriasis in Study 2



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#



# PASI response percent responders 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.

### Paediatric patients with plaque psoriasis

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

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

#### Paediatric Plaque Psoriasis Outcomes at 12 Weeks

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

Abbreviation: sPGA-static Physician Global Assessment.

a.  $p < 0.0001$  compared with placebo.

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

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

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

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

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

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

### Immunocompetence

Evaluations of immunocompetence were performed on 49 ENBREL-treated patients with active RA. No evidence of immunosuppression was found in evaluations of delayed-type hypersensitivity skin testing,

enumeration of immune effector cell populations and immunoglobulins and *in vitro* testing of neutrophil and T cell function.

### **Antibodies**

Antibodies to ENBREL, all non-neutralising, were detected in 4 out of 96 RA patients who received ENBREL at a dose of 25 mg twice a week for up to 3 months in a placebo-controlled trial. Results from JIA patients were similar to those seen in adult RA patients treated with ENBREL. No apparent correlation of antibody development to clinical response or adverse events was seen. Of 98 patients with psoriatic arthritis who have been tested, no patient has developed antibodies to ENBREL. Among 175 ankylosing spondylitis patients treated with ENBREL, 3 patients were reported with antibodies to ENBREL, none were neutralising. In double-blind studies up to 6 months duration in plaque psoriasis, about 1% of the 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.
- Treatment of chronic, severe plaque psoriasis in children and adolescents from 4 to 17 years, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. Duration of therapy to be no longer than 24 weeks and treatment to be ceased after 12 weeks if a significant PASI response is not achieved.

### **CONTRAINDICATIONS**

1. Known hypersensitivity to etanercept or to any of its excipients.
2. Patients with, or at risk of, sepsis.
3. Treatment with ENBREL should not be initiated in patients with serious, active infection including chronic or localised infections.
4. Concurrent treatment with Interleukin-1 antagonists.

### **PRECAUTIONS**

#### **Infections**

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

Serious infections including sepsis and tuberculosis, have been reported with the use of ENBREL. 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 appropriate 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 patients 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-glycosylated 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). Additionally, there have been very rare reports of peripheral demyelinating polyneuropathies (including Guillain-Barré syndrome). 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**

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

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

### **Monitoring**

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

### **Immunosuppression and carcinogenicity**

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.

Melanoma and non-melanoma skin cancer (NMSC) have been reported in patients treated with TNF-antagonists including ENBREL. Postmarketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with etanercept. Periodic skin examination is recommended for all patients who are at increased risk for skin cancer. Combining the results of controlled portions of clinical trials of ENBREL, more cases of non-melanoma skin cancer were observed in patients taking ENBREL compared with control patients, particularly in patients with psoriasis. Long-term animal studies have not been conducted to evaluate the carcinogenic potential of ENBREL.

### **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**

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

### **Fertility**

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

### **Use in pregnancy**

Category B2

The safe use of 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.

### **Paediatric use**

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.

Malignancies, some fatal have been reported among children, adolescents and young adults who received treatment with TNF-blocking agents (initiation of therapy at  $\leq 18$  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.

### **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.

### **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.

## **INTERACTIONS WITH OTHER MEDICINES**

### **Methotrexate**

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

### 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.

<b>Effect of Digoxin on pharmacokinetic parameters of Etanercept</b>		
Mean (SD)	Etanercept	Etanercept + Digoxin
C <sub>max</sub> (µg/mL)	2.64 (1.24)	2.53 (1.93)
AUC <sub>(0-t)</sub> (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.

<b>Effect of Warfarin on pharmacokinetic parameters of Etanercept</b>		
Mean (SD)	Etanercept	Etanercept + Warfarin
C <sub>max</sub> (µg/mL)	3.5 (1.09)	3.09 (1.22)
AUC <sub>(0-t)</sub> (µg/mL.h)	180 (71.9)	160 (75.1)

### Other

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

## ADVERSE EFFECTS

### Injection site reactions

Patients with rheumatic diseases in controlled trials treated with ENBREL had a significantly higher incidence (37% cf. 10%) of injection site reactions (erythema and/or itching, pain 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 carcinogenicity).

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

## **Autoantibody formation**

In controlled trials, the percentage of patients who developed new positive antinuclear antibodies (ANA) ( $\geq 1:40$ ), 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<sup>a</sup>**

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 <sup>b</sup>	32	38	1.54	1.50
Upper respiratory infection <sup>b</sup>	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:  $\geq 10\%$

Common:  $\geq 1\%$  and  $< 10\%$

Uncommon:  $\geq 0.1\%$  and  $< 1\%$

Rare:  $\geq 0.01\%$  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

Rare

Melanoma

Unknown

Merkel cell carcinoma

<b>System</b>	<b>Adverse Reaction</b>
<b>Infections and Infestations</b>	
Very Common	Infections (including upper respiratory tract infections, bronchitis, cystitis, skin infections)†
Common	Serious infections (including pneumonia, cellulitis, septic arthritis, sepsis)†
Rare	Tuberculosis
<b>Immune System Disorders</b>	
Common	Allergic reactions; autoantibody formation
Rare	Serious allergic/anaphylactic reactions (including angioedema, bronchospasm)
Uncommon	Systemic vasculitis (including ANCA positive vasculitis)
Not known	Macrophage activation syndrome, sarcoidosis
<b>General Disorders and Administration Site Conditions</b>	
Common	Fever
<b>Respiratory, Thoracic and Mediastinal Disorders</b>	
Uncommon	Interstitial lung disease (including pulmonary fibrosis and pneumonitis)
<b>Nervous System Disorders</b>	
Rare	Seizures, CNS demyelinating events including multiple sclerosis and localized demyelinating conditions such as optic neuritis and transverse myelitis
<b>Eye Disorders</b>	
Uncommon	Uveitis
<b>Skin and Subcutaneous Tissue Disorders</b>	
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
<b>Musculoskeletal, Connective Tissue and Bone Disorders</b>	
Rare	Subacute cutaneous lupus erythematosus, discoid lupus erythematosus, lupus-like syndrome
<b>Cardiac Disorders</b>	
Rare	Worsening of congestive heart failure
<b>Hepatobiliary Disorders</b>	
Rare	Elevated liver enzymes, autoimmune hepatitis
†see additional information, under “Infections” above.	
†† See additional information under “Psoriasis” above.	

### **Paediatric patients with juvenile idiopathic arthritis**

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

JIA patients treated with ENBREL 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.

### **Paediatric patients with plaque psoriasis**

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

## DOSAGE AND ADMINISTRATION

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

### Adults

#### *Rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis*

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

#### *Plaque psoriasis*

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

### Elderly patients

Elderly RA patients (age  $\geq$  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

#### *Juvenile idiopathic arthritis (age 4 years and above)*

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.

#### *Paediatric plaque psoriasis (age 4 years and above)*

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

### Instructions for use, handling and disposal

#### *Reconstitution (Powder for injection only)*

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

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

Visually inspect the solution for particulate matter and discolouration prior to administration. The solution should not be used if discoloured or cloudy, or if particulate matter remains. Withdraw the solution into the empty syringe, removing only the dose to be given from the vial. Some foam or bubbles may remain in the vial. Do not filter reconstituted solution during preparation or administration. Do not use ENBREL if all the powder in the vial is not dissolved within 10 minutes. Start again with another vial. Once the ENBREL solution has been aspirated into the syringe, discard the vial adaptor and replace with a needle from the pack for injection. 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 (approximately 15 to 30 minutes). Immediate use is then recommended. The needle cover should not be removed while allowing the Auto-injector to reach room temperature. By looking through 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<sup>2</sup> followed by SC doses of 16 mg/m<sup>2</sup> 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 overdose, please contact the Poisons Information Centre on 131 126.

## **PRESENTATION AND STORAGE CONDITIONS**

### **Powder for injection**

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

ENBREL powder for injection cartons contain 4 clear glass vials (4 mL, Type 1 glass) with Teflon coated rubber stoppers, aluminium seals and flip-off plastic caps. ENBREL is also supplied with 4 pre-filled



syringes containing 1 mL water for injections and 8 alcohol swabs. The pre-filled syringes are also made of Type 1 glass. Four vial adaptors and four 27 gauge needles are provided in the carton.

\* not marketed

#### **Pre-filled syringe (Solution for injection)**

ENBREL solution for injection is supplied in a kit containing four single-dose pre-filled glass syringes containing ENBREL solution. Each syringe of ENBREL contains either 25 mg\* (in 0.5 mL) or 50 mg (in 1 mL) of the active ingredient, etanercept (rch). The needle cover contains natural rubber (latex). Four alcohol swabs are also 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 2, 4 or 12 alcohol swabs.

\* not marketed

#### **Storage**

Powder for injection

Store at 2°C 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 2°C 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.

#### **NAME AND ADDRESS OF THE SPONSOR**

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

® Registered Trade Mark

#### **POISON SCHEDULE OF THE MEDICINE**

S4, PRESCRIPTION ONLY MEDICINE.

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