



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Dermatologic and Ophthalmic Drugs Advisory Committee
June 18, 2008

Enbrel (etanercept) for the Treatment of Pediatric Plaque Psoriasis

Enbrel is a soluble tumor necrosis factor (TNF) receptor fusion protein that binds TNF- α . Enbrel was first approved by the FDA in 1998 for the treatment of adult rheumatoid arthritis, and is currently approved for the treatment of rheumatoid arthritis, polyarticular-course juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, and adult plaque psoriasis. Currently in the US, there are no approved systemic drugs for the treatment of psoriasis in children or adolescents.

The 2004 BLA application for adult plaque psoriasis did not contain data on the use of etanercept in children, and a post-marketing commitment was included in the Approval letter for the applicant to evaluate safety and efficacy of etanercept in pediatric subjects with plaque psoriasis.

The applicant has conducted a placebo-controlled multicenter study in 211 pediatric subjects with plaque psoriasis (Study Number 20030211) to fulfill the 2004 post-marketing commitment.

In general, applicants for systemic products have requested and received a waiver, partial waiver or deferral for pediatric studies required by the Pediatric Research Equity Act (reauthorized by FDAAA in September, 2007).

Specifically, the committee will be asked to provide advice and recommendations on the issues detailed below:

Information needed for approval: Information submitted to support the indication for pediatric plaque psoriasis includes data from 211 subjects with moderate to severe psoriasis. The patient population studied for this application includes a preponderance of older and heavier patients. The Committee should consider whether or not the applicant has provided sufficient information to approve the use of etanercept in pediatric plaque psoriasis, a chronic condition that may wax and wane.

Risk of malignancy/life threatening infections: Etanercept has the potential for life threatening infections and carries a boxed warning describing this risk. Recently available information describes malignancies in pediatric patients with juvenile idiopathic arthritis and other conditions treated with etanercept. The Committee will need to consider whether the benefits of etanercept outweigh the risks for

pediatric patients with plaque psoriasis, or whether these safety concerns may preclude approval for pediatric psoriasis until additional safety data is obtained.

Developing immune system: There appears to be an informational need to describe the long-term safety of etanercept and its effect on the developing immune system. The effects of chronic immunosuppression on the immune system of children with etanercept, such as maintenance of vaccine response and immune mediated hematologic effects are unknown. Post-marketing drug usage estimates for etanercept illustrate limited experience in the pediatric population (for both time and extent), so conclusions regarding effects on immune system development and physical growth are not yet possible.

Maintenance of response over time: Maintenance of treatment effect was evaluated in a 12 week withdrawal/retreatment phase of this study. In subjects who received etanercept throughout the trial over the 48 week period, it was noted that the treatment response decreased over time. Questions are raised regarding the durability of response and the potential for risks associated with prolonged treatment with this potent immunosuppressant.

The Committee will be asked to consider whether the results from this study provide an adequate risk-benefit to support etanercept for the treatment of plaque psoriasis in pediatric patients and to specifically make recommendations for approval of this application. The Committee will be asked to consider the extent to which the known and potential risks can be minimized or managed, and whether the expected risks in clinical practice are commensurate with the benefits achieved.

Etanercept for Treatment of Pediatric Plaque Psoriasis
FDA DODAC Meeting
June 18, 2008

I. Plaque Psoriasis in Pediatric Patients

Plaque psoriasis is a chronic T-lymphocyte mediated inflammatory skin disease characterized by erythematous plaques with silvery-white scales. Psoriasis plaques are characterized by keratinocyte hyperproliferation, vascular endothelial proliferation and inflammatory cell infiltration. The most common form of psoriasis in children is plaque psoriasis.

The National Center for Health Statistics of the Centers for Disease Control and Prevention estimated in 1996 that the prevalence of the disease in children under the age of 18 was 0.32%. Of affected children, 2% of cases begin in the first two years of life and 10% are diagnosed before the age of 10 years. A recent study in the United Kingdom indicates that the prevalence of psoriasis among those 0-9 years of age is 0.55% and 10 to 19 years of age is 1.37% (Gelfand, 2005).

Plaque psoriasis usually follows an irregular, chronic course marked by remissions and exacerbations of unpredictable onset and duration. In most pediatric cases the disease is relatively mild, typically confined to localized cutaneous regions, and treatment with topical agents is usually sufficient (Benoit, 2007, Paller and Mancini, 2006).

Non-cutaneous manifestations associated with pediatric psoriasis may include psoriatic arthritis and psoriatic uveitis. Both are rare in childhood, but severe cases can be rapidly progressive and incapacitating. There is no relationship between the severity of the cutaneous disease and the development of the joint disease. Either the skin disease or the arthritis may develop initially, and the flares of joint and skin disease are not usually correlated (Paller and Mancini, 2006).

II. Pediatric Psoriasis Treatment

The mainstay of treatment for most psoriasis patients regardless of age is topical therapy. Emollients are used to decrease scaling and itching, and may be sufficient in mild cases. The most commonly used treatment is topical corticosteroids. Labeling for some topical corticosteroids include provisions for use in patients of pediatric age.

Other commonly used topical agents include calcipotriene (a vitamin D analogue), tazarotene (a retinoid) and anthralin. Salicylic acid is used as a keratolytic agent. Skin irritation is the most common adverse effect of these topical agents. The safety and efficacy of tazarotene cream have not been established in patients with psoriasis under the age of 18 years, nor have safety and effectiveness of calcipotriene in pediatric patients been specifically established.

Phototherapy for psoriasis includes UVB, narrow band UVB, and psoralen, a photosensitizer, plus UVA (PUVA). PUVA induces responses in a high proportion of patients and can induce long-term remissions. PUVA treatment increases the risk of cutaneous malignancy in a dose-related fashion.

There is no approved systemic therapy for the treatment of plaque psoriasis in the pediatric population. Systemic therapy for treating childhood psoriasis is generally reserved for the most severe plaque psoriasis recalcitrant to topical therapies or pustular and erythrodermic (exfoliative) psoriasis which are the most severe variants of childhood psoriasis.

Methotrexate, cyclosporine, and retinoids (acitretin) are used in the treatment of pediatric psoriasis. For methotrexate, safety and effectiveness in pediatric patients have been established only in cancer chemotherapy and in polyarticular-course juvenile rheumatoid arthritis. The safety and efficacy of Neoral[®] (cyclosporine) treatment in children with juvenile rheumatoid arthritis or psoriasis below the age of 18 have not been established. Cyclosporine, an immunosuppressant calcineurin inhibitor, can induce hypertension, nephrotoxicity, increased risk of malignancy (especially B cell lymphoma) and infection. Acitretin is approved for severe psoriasis in adults.

While immunosuppressant biologic therapies other than etanercept including alefacept (an LFA3-Ig fusion protein), efalizumab (a monoclonal antibody to CD11a), infliximab (chimeric monoclonal antibody) and adalimumab (a monoclonal antibody) are licensed for the treatment of moderate to severe plaque psoriasis in adults, no biologic therapies are licensed with an indication for treatment of psoriasis in children. As with other immunosuppressants, these products are associated with an increased risk of infection and malignancy in addition to other warnings related to use of these therapies as described in each product label.

III. Etanercept (Enbrel)

Etanercept is a dimeric fusion protein of the extracellular ligand-binding portion of the human 75 kiloDalton tumor necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1. Etanercept binds specifically to tumor necrosis factors (TNF) α and β to block their interaction with cell surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses and is thought to play an important role in the inflammatory processes of rheumatologic diseases and plaque psoriasis.

Enbrel (etanercept) was licensed in the United States on November 2, 1998 and at present is indicated for:

- Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis. For this indication Enbrel

can be initiated in combination with methotrexate or used alone. (Initial approval November 2, 1998; Revised June 6, 2000; July 24, 2003) [Studies submitted involved only subjects \geq 18 years of age.]

- Reducing signs and symptoms of moderately to severely active polyarticular-course juvenile idiopathic arthritis in patients ages 2 and older. (Initial approval May 27, 1999)
- Reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with psoriatic arthritis. Enbrel can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone. (Initial approval January 15, 2002; revised August 21, 2003) [Subjects in submitted studies were between 18 and 70 years of age.]
- Reducing signs and symptoms in patients with active ankylosing spondylitis. Initial approval July 24, 2003) [Subjects in submitted studies were between 18 and 70 years of age.]
- The treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. [Label specifies “The safety and efficacy of Enbrel in pediatric patients with plaque psoriasis have not been studied.”]

The drug is supplied in pre-filled syringes and multiple use vials of lyophilized etanercept for reconstitution and is administered weekly by subcutaneous injections.

The 2004 application for the treatment of plaque psoriasis in adults did not contain data on the use of etanercept in children, and the approval letter issued in April 2004 contained the post-marketing commitment for the applicant to conduct a placebo controlled multi-center study to determine safety and efficacy of etanercept in pediatric subjects with plaque psoriasis. The Agency approval letter of April 30, 2004 for adult psoriasis defined a pediatric post-marketing commitment as follows:

To conduct study protocol 20030211, a 48 week, 200 pediatric patient, multicenter placebo-controlled clinical trial, to determine the safety and efficacy of etanercept in pediatric patients, 4 to 17 years of age, with chronic plaque psoriasis. The final study protocol will be submitted August 31, 2004, the study will be initiated by December 31, 2004, patient accrual will be completed by December 31, 2005, the study will be completed by December 31, 2006, and the final study report with revised labeling if applicable, will be submitted by September 30, 2007.

The applicant, Amgen Inc., on behalf of Immunex Corporation, has submitted the results of that study and proposes to add a new indication for the treatment of chronic moderate to severe plaque psoriasis in pediatric patients who are inadequately controlled with

topical psoriasis therapy or who have received systemic therapy or phototherapy. The pediatric population was defined as patients 4 -17 years of age.

For systemic products for the treatment of plaque psoriasis, in general the applicants have requested a waiver or partial waiver for pediatric studies required by the Pediatric Research Equity Act (2003, reauthorized by FDAAA in September, 2007).

At the request of an applicant, FDA would typically grant a full waiver, partial waiver or deferral for pediatric assessments if the applicant certifies and FDA finds one or more of the following acceptable:

- (a) Necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed) (section 505B(a)(4)(A)(i) of the Act).
- (b) There is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups (section 505B(a)(4)(A)(ii) of the Act).
- (c) The drug or biological product (1) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, and (2) is not likely to be used in a substantial number of pediatric patients (section 505B(a)(4)(A)(iii) of the Act).

Some of the other sponsors of biologic drug products for psoriasis have referred to both (a) and (b) in formal requests for waiver of pediatric studies.

IV. Pediatric Plaque Psoriasis Trial 20030211-Efficacy

One trial was submitted in support of the proposed new indication for the treatment of pediatric plaque psoriasis.

In this randomized, double-blind, placebo-controlled trial, etanercept was compared to placebo for an initial 12 week period. This was followed by a 24 week, open label treatment phase in which all subjects were treated with etanercept. The final twelve weeks involved a randomized, double-blind withdrawal-retreatment phase to examine the effects of withdrawal of etanercept therapy and subsequent retreatment.

Enrolled were 211 pediatric subjects 4 to 17 years of age with moderate to severe stable plaque psoriasis, defined as a Static Physician's Global Assessment of Psoriasis (sPGA) score ≥ 3 ("Moderate") with a body surface area involvement $\geq 10\%$ and a PASI (psoriasis area-and-severity index) score ≥ 12 at baseline. Subjects must also have been treated with phototherapy or systemic psoriasis therapy and/or must have been considered poorly controlled with topical therapy.

Within each age stratum, subjects were randomized to either etanercept 0.8 mg/kg once weekly up to maximum dose of 50 mg once weekly or placebo in a 1:1 ratio. 106 and 105 subjects were randomized to etanercept and placebo arms, respectively. The enrollment of the 4 to 11 year old group was 76 (36%) subjects. Median weight for enrolled children was 61.8 kilograms and the median height was 155.34 centimeters.

The treatment regimen for each period:

- Period A (12 weeks): Double-blind, placebo-controlled treatment period

Subjects randomized to receive either placebo or etanercept 0.8 mg/kg (up to maximum dose of 50mg) once weekly (QW);

At or after Week 4, subjects with >50% increase or an absolute increase of at least 4 points in PASI score from baseline were allowed to enter an escape arm to receive open-label etanercept QW through Week 12.

- Period B (24 weeks): Open-label treatment period

All subjects, including those in the escape arm, were to enter the open-label treatment period to receive etanercept QW through the Week 36.

At the Week 24 visit, subjects who achieved a PASI 50 response were to remain in the open-label treatment arm. Those who did not achieve a PASI 50 response were given the option to discontinue the study or to enter the incomplete-responder arm. Subjects in the incomplete-responder arm had the option to receive topical psoriasis therapy according to the standard of care in addition to receiving open-label etanercept.

- Period C (12 weeks): Randomized double-blind withdrawal-retreatment period

Subjects who achieved a PASI 75 response at Week 36 were re-randomized to placebo or etanercept QW.

Subjects who did not achieve a PASI 75 response at Week 36 were given the option to discontinue the study or enter the incomplete-responder arm. Incomplete-responders were to continue to receive etanercept QW until the end of the study and had the additional option of receiving standard of care topical treatment.

Subjects who entered the incomplete-responder arm in Period B were not eligible for randomization in Period C.

Period A was designed to evaluate the therapeutic effect of etanercept and Period C to evaluate disease relapse and durability of response. Clinical evaluations were conducted at Baseline, Weeks 2, 4, 8, and 12 in Period A and every 4 weeks in Periods B and C.

The primary efficacy endpoint was defined as a 75% or greater improvement from baseline in the psoriasis area-and-severity index (PASI 75) at week 12. The secondary endpoints included PASI 50, PASI 90, physician's global assessment of clear or almost clear of disease, CDLQI assessments, and safety assessments.

PASI is an acronym for Psoriasis Area Severity Index and is a scoring system that is calculated based upon the severity of signs of psoriasis for various anatomical locations and an estimated body surface area. PASI is an assessment of disease severity that can range from 0.0 to 72.0. This complex assessment, which is used in clinical studies, but rarely in clinical practice, compiles assessments of head, trunk and extremity involvement with severity of erythema, infiltration, and desquamation as described below:

Four anatomic sites - head, upper extremities, trunk, and lower extremities - are assessed for erythema, induration (plaque thickness), and desquamation (scaling) as seen on the day of the examination. The severity of each sign is assessed using a 5-point scale:

- 0 = No symptoms
- 1 = Slight
- 2 = Moderate
- 3 = Marked
- 4 = Very marked

The below table outlines the characteristics of each category.

	Erythema^a	Desquamation	Induration
0=none	No redness	No scaling	No elevation over normal skin
1=slight	Faint redness	Fine scale partially covering lesions	Slight but definite elevation, typically edges indistinct or sloped
2=moderate	Red coloration	Fine to coarse scale covering most of all of the lesions	Moderate elevation with rough or sloped edges
3=marked	Very or bright red coloration	Coarse, non-tenacious scale predominates covering most or all of the lesions	Marked elevation typically with hard or sharp edges
4=very marked	Extreme red coloration; dusky to deep red coloration	Coarse, thick, tenacious scale over most or all lesions; rough surface	Very marked elevation typically with hard sharp edges

a. Do not include residual hyperpigmentation or hypopigmentation as erythema.

The area affected by psoriasis within a given anatomic site is estimated as a percentage of the total area of that anatomic site and assigned a numerical value according to the degree of psoriatic involvement as follows:

- 0 = no involvement
- 1 = <10%
- 2 = 10 to <30%
- 3 = 30 to <50%
- 4 = 50 to <70%
- 5 = 70 to <90%
- 6 = 90 to 100%

Assignments for the following body regions are as follows:

- Neck: include with the head
- Buttocks: include with the lower extremities
- Axillae: include with the trunk
- Genitals: include with the trunk
- The inguinal canal separates the trunk and legs anteriorly

The PASI score for each body region is obtained by multiplying the sum of the severity scores by the area score, then multiplying the result by the constant weighted value assigned to that body region. Since the head, upper extremities, trunk, and lower extremities correspond to approximately 10, 20, 30, and 40% of body surface area, respectively, the PASI score is calculated using the formula:

$$\text{PASI} = 0.1(E_h + I_h + D_h)A_h + 0.2(E_u + I_u + D_u)A_u + 0.3(E_t + I_t + D_t)A_t + 0.4(E_l + I_l + D_l)A_l$$

where E , I , D , and A denote erythema, induration, desquamation, and area, respectively, and h , u , t , and l denote head, upper extremities, trunk, and lower extremities, respectively. PASI scores range from 0.0 to 72.0 with the highest score representing complete erythroderma of the severest degree.

To supplement the PASI scoring system, a physician's global assessment for psoriasis severity was also used.

The sPGA (Static Physician's Global Assessment of Psoriasis) for the submitted study was defined as the following:

0	Clear, except for residual discoloration
1	Majority of lesions have individual score for induration, erythema and scaling (IES) that averages 1
2	Majority of lesions have individual score for induration, erythema and scaling (IES) that averages 2
3	Majority of lesions have individual score for induration, erythema and scaling (IES) that averages 3
4	Majority of lesions have individual score for induration, erythema and scaling (IES) that averages 4
5	Majority of lesions have individual score for induration, erythema and scaling (IES) that averages 5

Induration

- 0 no evidence of plaque elevation
- 1 minimal plaque elevation, w 0.5 mm
- 2 mild plaque elevation, ~ 1 mm of the lesion
- 3 moderate plaque elevation, ~ 1.5 mm
- 4 marked plaque elevation, ~ 2 mm
- 5 severe plaque elevation, ~ 2.5 mm

Erythema

- 0 no evidence of erythema, hyperpigmentation may be present
- 1 faint erythema
- 2 light red coloration
- 3 moderate red coloration
- 4 bright red coloration
- 5 dusky to deep red coloration

Scaling

- 0 no evidence of scaling
- 1 minimal; occasional fine scale over less than 5%
- 2 mild; fine scale predominates
- 3 moderate; coarse scale predominates
- 4 marked; thick, non-tenacious scale predominates
- 5 severe; very thick tenacious scale predominates

At week 12, 57% of subjects who received etanercept (60 of 106) achieved a PASI score of 75 compared to 11% of those who received placebo (12 of 105). The proportions of subjects who achieved a score of 0 or 1 on the sPGA was also greater 53% in the etanercept group (56 of 106) compared with 13% in the placebo group (14 of 105).

Primary Efficacy Results (ITT)
Number (%) of Successes on sPGA Score and PASI 75 at Week 12

	Etanercept n=106	Placebo n=105
sPGA		
Number of successes (%)	55 (51.9%)	14 (13.3%)
p-value [†]		<0.0001
PASI 75		
Number of successes (%)	60 (56.6%)	12 (11.4%)
p-value [†]		<0.0001

[†] P-value was calculated using CMH test, stratified by age group.

All missing values were imputed as failures

The proportions of subjects who achieved a response defined as PASI 50 response and PASI 90 response at week 12 were also greater than those who took placebo.

Number of Subjects Who Achieved Success in PASI 50/90/100 at Week 12

	Etanercept n=106	Placebo n=105
PASI 50	79 (74.5%)	24 (22.9%)
PASI 90	29 (27.4%)	7 (6.7%)
PASI 100	7 (6.6%)	2 (1.9%)

All missing values were imputed as failures.

Source: Agency Analysis

At week 12, short term efficacy of etanercept was demonstrated based on PASI 75 response and sPGA response. During the 24 week Period B, subjects were then either started on etanercept or continued on etanercept such that all subjects were to be

treated with etanercept during Period B and were evaluated every 4 weeks during treatment.

Finally, subjects who maintained success based on PASI 75 response at Week 36 were re-randomized to either etanercept or placebo for a 12-week randomized withdrawal period (Period C). In this period, maintenance of efficacy was evaluated at Weeks 40, 44 and 48 based on the sPGA score and PASI 75.

V. Pediatric Plaque Psoriasis Trial 20030211- Safety

210 subjects received at least one dose of etanercept, and 194 (92%) completed the 48 week study.

There were no deaths in the trial, and no serious adverse events in the initial placebo controlled phase (12 weeks).

Four serious adverse events were observed during the open label phase: a 7 year old girl with LLL pneumonia with effusion and negative blood culture requiring hospitalization and intravenous antibiotics; a 9 year old with gastroenteritis and dehydration requiring hospitalization for one day for intravenous fluids; and a 14 year old with a hemorrhagic ovarian cyst requiring surgical removal.

The case of pneumonia and the case of gastroenteritis were the only serious infections during the trial. No malignancies, opportunistic infections, tuberculosis, or demyelinating disease were reported.

During the initial 12-week double-blind period, the proportions of subjects reporting adverse events or infections were slightly higher in the etanercept 0.8 mg/kg QW group (64.2%) than the placebo (59.0%) group. The most common events during the double-blind period were upper respiratory tract infection and headache.

Adverse Events that Occurred in at Least 3% of Subjects (Period A)

Preferred Term	Etanercept	Placebo
	n=106	n=105
Headache	18 (17.0%)	18 (17.1%)
Upper respiratory tract infection	18 (17.0%)	13 (12.4%)
Nasopharyngitis	10 (9.5%)	10 (9.5%)
Influenza	8 (7.5%)	3 (2.9%)
Arthralgia	7 (6.6%)	0
Dizziness	6 (5.7%)	1 (1.0%)
Gastroenteritis	6 (5.7%)	0
Injection site pain	6 (5.7%)	0
Vomiting	5 (4.7%)	2 (1.9%)
Cough	4 (3.8%)	2 (1.9%)
Pharyngolaryngeal pain	1 (<1%)	6 (5.7%)
Pharyngitis	2 (1.9%)	5 (4.8%)
Diarrhoea	1 (<1%)	4 (3.8%)
Injection site bruising	1 (<1%)	4 (3.8%)

Source: Reviewer analysis.

Seventeen etanercept subjects reported 23 events of streptococcal pharyngitis while one subject from the placebo group reported one event of strep. There were 15 events of gastroenteritis in 13 subjects. All were exposed to etanercept. All cases were mild to moderate in severity with the exception of one case, which was assessed as severe due to hospitalization for intravenous fluids.

VI. Issues for Discussion

1. Does this single trial with a population of 211 subjects provide sufficient efficacy and safety information to support approval for an indication of treatment of pediatric plaque psoriasis?

- The safety database is limited:
 - i) 211 subjects were studied, with age of inclusion skewed towards the older children
 - ii) only 31 subjects received etanercept treatment for the 48 week duration

For this study population, even though subjects were required to have a PGA ≥ 3 , a BSA $\geq 10\%$, and a PASI ≥ 12 at baseline, the median baseline PASI was 16 and 43% of subjects had no previous systemic or photo therapy history. Only 3% (6 of 211) of subjects had a PGA of 5 (severe).

Static Physician Global Assessment of Psoriasis at Baseline			
PGA Score	Placebo (105)	Etanercept (106)	All (211)
Unknown	0 (0)	0 (0)	0 (0)
0	0 (0)	0 (0)	0 (0)
1	0 (0)	0 (0)	0 (0)
2	1 (1)	1 (1)	2 (1)
3	68 (65)	69 (65)	137 (65)
4	33 (31)	33 (31)	66 (31)
5	3 (3)	3 (3)	6 (3)

- Subjects included in this study had higher body weight and BMI than aged-matched peers.

Age Groups:	Placebo Subjects	Etanercept Subjects	All Subjects
4-11	38 (36%)	38 (36%)	76 (36%)
12-17	67 (64%)	68 (64%)	145 (64%)

Mean Weights of Subjects			
Ages	4-11	37 kg = 81 lbs	(range 37-169 lbs)
Ages	12-17	75 kg = 165 lbs	(range 83-363 lbs)

National Center for Health Statistics Reference US Mean Weights:					
		Boys		Girls	
Age	4	16 kg	35 lbs	16 kg	35 lbs
	8	26 kg	57 lbs	27 kg	59 lbs
	12	41 kg	90 lbs	42 kg	92 lbs
	16	61 kg	134 lbs	54 kg	119 lbs

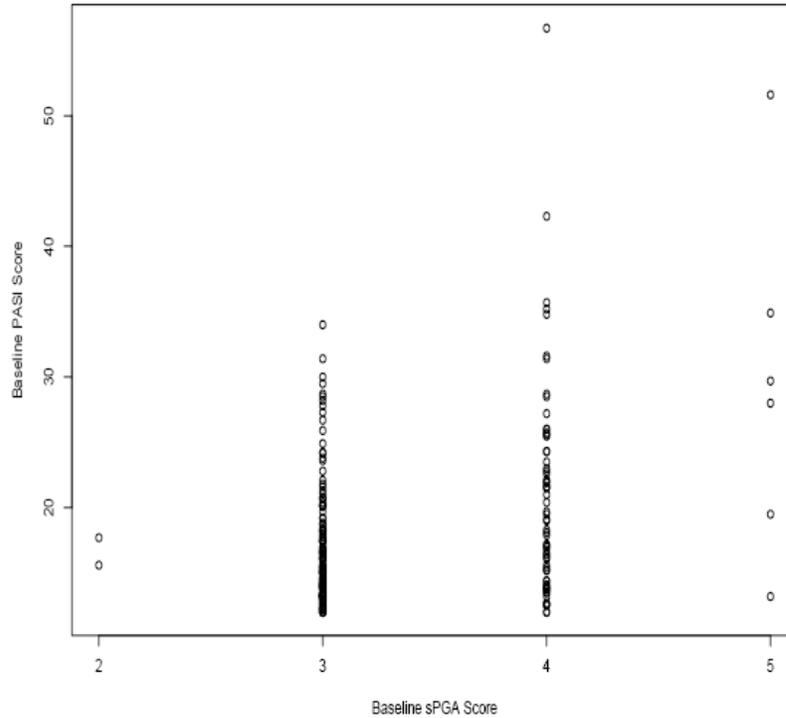
Mean BMI of Subjects:	
Ages 4-11	19.8
Ages 12-17	27.01

National Center for Health Statistics Reference BMI Ranges:	
Age	BMI
4	15.5
8	16
18	20.5
20	22
Overweight in adults	25-29.9
Obese in adults	30 or higher

- There appears to be little direct correlation between sPGA and PASI, especially with disease of higher baseline severity. The 6 patients described

with a Physician’s Global Assessment of 5 (or Severe) at baseline had PASIs ranging from 13 to 51. This illustrates the limited number of patients enrolled with a baseline sPGA score of 5.

Baseline PGA Assessments Compared with Baseline PASI Scores



- The table below illustrates the range of PASI responses at week 12.

Number of Subjects Who Achieved Success in PASI 50/90/100 at Week 12

	Etanercept n=106	Placebo n=105
PASI 50	79 (74.5%)	24 (22.9%)
PASI 90	29 (27.4%)	7 (6.7%)
PASI 100	7 (6.6%)	2 (1.9%)

All missing values were imputed as failures.

- The table below illustrates the number of subjects maintaining a PASI 75 between 36 and 48 weeks. The efficacy response appears to wane over time despite continued treatment with Enbrel. Subjects who received etanercept treatment over the third stage of the trial had decreasing response over time when subjects who entered the escape arm were treated as failures.

Number of Subjects (%) that Maintain Successes in sPGA and PASI 75 over Time

Table 1: Number of Subjects (%) that Maintain Success Status in sPGA and PASI 75 Over Time

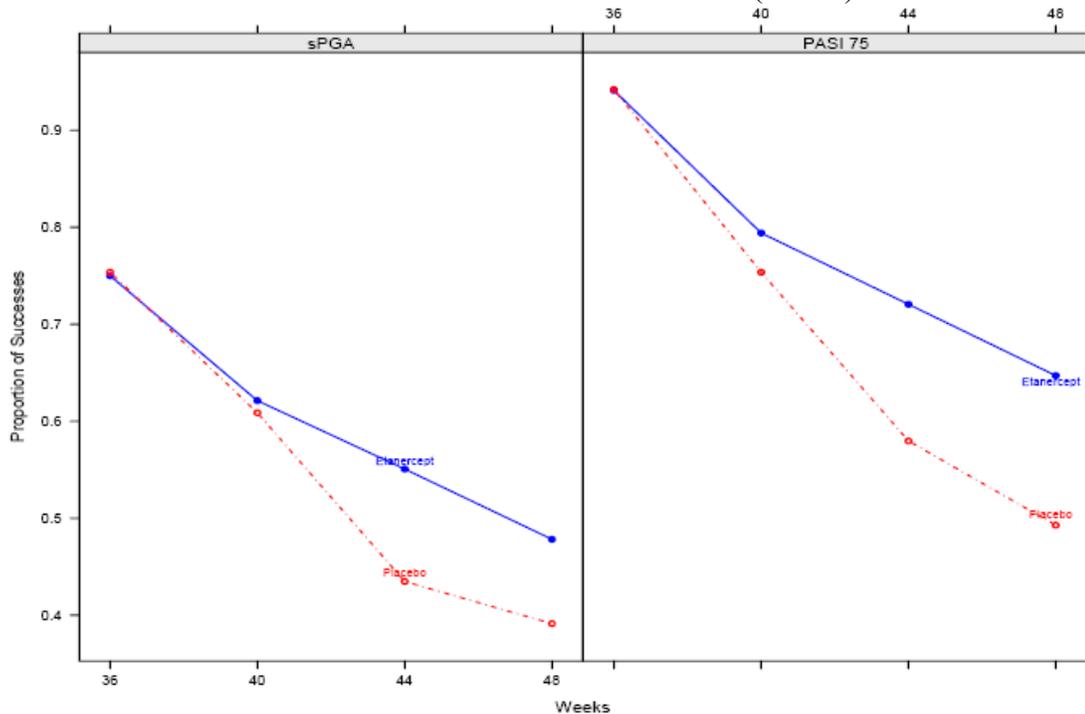
Endpoint	Week	Etanercept n=68	Placebo n=69
sPGA	36	51 (75.0%)	52 (75.4%)
	40	41 (62.1%)	42 (60.9%)
	44	38 (55.1%)	30 (43.5%)
	48	33 (47.8%)	27 (39.1%)
PASI 75	36	64 (94.1%)	65 (94.2%)
	40	54 (79.4%)	52 (75.4%)
	44	49 (72.1%)	40 (58.0%)
	48	44 (64.7%)	34 (49.3%)

All missing values were imputed as failures.

Source: Reviewer analysis.

The plots below illustrate a comparison of efficacy response over time for etanercept versus placebo for weeks 36 to 48. The data indicate that there is a decrease in the number of patients demonstrating success in both arms. While the decrement in the placebo arm would be anticipated, the reason for the apparent decrease in etanercept efficacy in Period C is unclear.

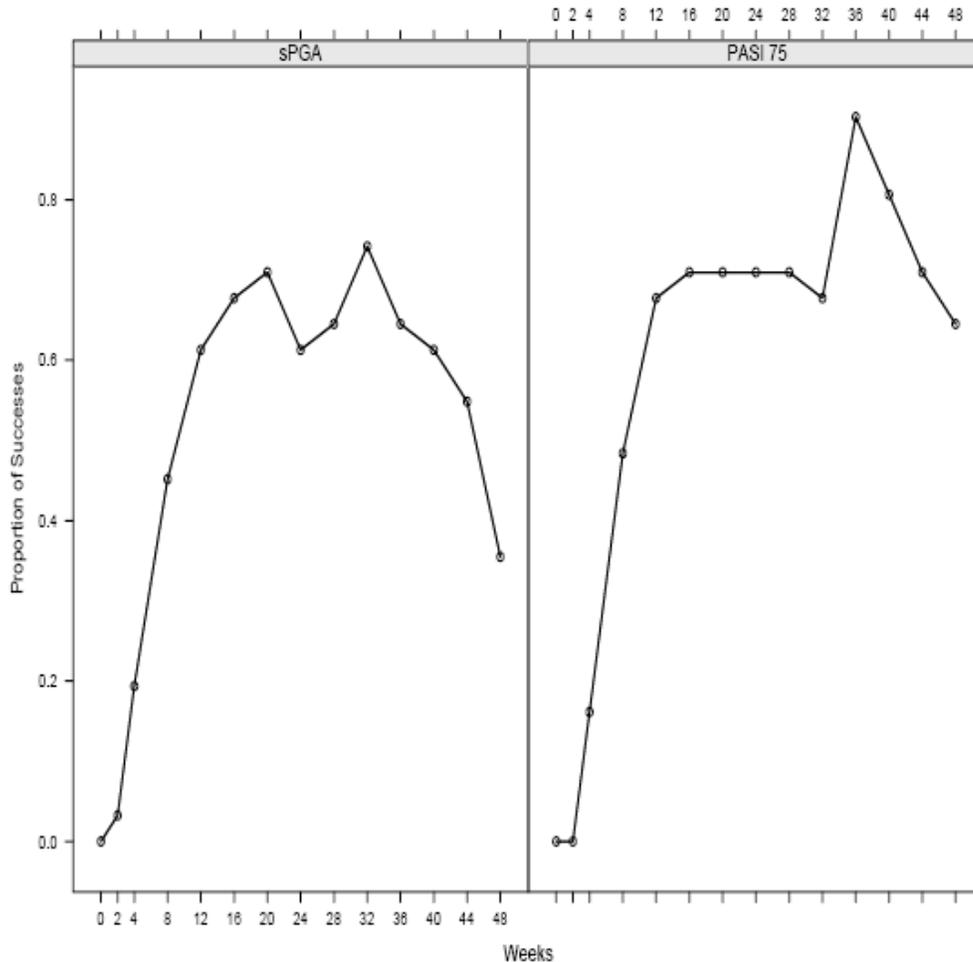
Maintenance of Efficacy - Results over Time (Week 36 to Week 48) with Randomization to Placebo vs. Continued Enbrel Treatment (n=137)



Source: Agency Analysis

The graphs below depicts the subset of subjects (n=31) who received etanercept therapy for the entire 48 weeks.

Proportion of Successes in Subjects on Etanercept Treatment continued throughout 48 Weeks (n=31)



2. Is a treatment that can result in life-threatening infections, such as Enbrel, acceptable in this patient population for treatment of moderate to severe plaque psoriasis?

- Earlier this year, a boxed warning was added to the labeling for Enbrel (etanercept): “Infections, including serious infections leading to hospitalization or death, have been observed in patients treated with ENBREL...”

While only two serious infections were observed in the study population of 211 subjects from the one study conducted, there are concerns regarding the known potential of immunosuppressant anti-TNF agents to cause serious, life threatening infections.

The Agency recently reviewed all post-marketing pediatric cases retrieved from the Adverse Event Reporting System (AERS) with an outcome of death in patients receiving etanercept; and the majority (8 of 14 cases) occurred in pediatric patients who received etanercept for Juvenile Idiopathic Arthritis (JIA), which is the only approved indication for pediatric patients at this time. The most commonly reported cause of death was due to infectious complications. In addition, Agency review of serious domestic safety events in pediatric patients also showed that infections were the most commonly reported events that resulted in other serious outcomes, including hospitalizations and/or life-threatening outcomes.

- Use of anti-infective medication (antibiotic, antiviral, and antifungal medications) was slightly higher during both the double-blind 12 week phase as well as the open label phase.

	Etanercept		
	Placebo (N = 105)	0.8 mg/kg QW (N = 108)	All (N = 211)
Subjects who used at least one antibiotic, antiviral, or antifungal medication - n (%)	21 (20.0%)	27 (25.5%)	48 (22.7%)
Subjects who used at least one antibiotic medication - n (%)	20 (19.0%)	25 (23.6%)	45 (21.3%)
Subjects who used at least one systemic antibiotic medication - n (%)	17 (16.2%)	19 (17.9%)	36 (17.1%)
Subjects who used at least one antiviral medication - n (%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Subjects who used at least one systemic antiviral medication - n (%)	0 (0.0%)	1 (0.9%)	1 (0.5%)

	Etanercept		
	Placebo (N = 105)	0.8 mg/kg QW (N = 108)	All (N = 211)
Subjects who used at least one antifungal medication - n (%)	1 (1.0%)	1 (0.9%)	2 (0.9%)
Subjects who used at least one systemic antifungal medication - n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

3. What is the impact of the potential for carcinogenicity, associated with Enbrel therapy, on the benefit/risk in pediatric patients with psoriasis?

FDA post-marketing analysis describes nine malignancies (US 5, foreign 4) reported in pediatric patients who received etanercept. Three of nine were lymphoma cases in JIA patients. Although lymphoma has been associated in adults who received anti-TNF therapy (including etanercept), lymphoma is not a known complication of JIA.

Characteristics of Etanercept Pediatric AERS Cases of Malignancies
US and Foreign Cases from Marketing to April 14, 2008 (N=9)

Age distribution	Range - 10 to 18 years* Median - 17 years
Gender	Female - 4 Male - 4 Unknown - 1
Indication	JIA - 7 (+ psoriatic arthritis in one) Ankylosing spondylitis - 1 Unknown - 1
Time to onset (n=7)	Range - 29 days to 7 years Median - 2.5 years
Serious outcome due to malignancy	Hospitalization - 5 (+ life-threatening in one) Life-threatening - 2
Relevant co-suspect/concomitant immunosuppressants (n=6)	<ul style="list-style-type: none"> • Corticosteroid - 2 • MTX, corticosteroid - 2 (MTX co-suspect in one) • MTX - 1 (co-suspect) • MTX, azathioprine, corticosteroid - 1 (MTX & azathioprine were co-suspects)
Reported dose (n=5)	0.4 mg/kg - 1 25 mg - 4
Report type	Expedited (15-day) - 5 Periodic - 1 Direct - 1 From the sponsor submission - 2
Reporter	Physician - 6 Healthcare professional - 2 Consumer - 1
Source	US - 5 Foreign - 4 (3 registry reports)

The reported malignancies included one case each of Hodgkin's lymphoma, malignant lymphoma and acute myeloid leukemia (AML), diffuse B-cell non-Hodgkin's lymphoma (NHL), unspecified leukemia, myelodysplastic syndrome, papillary thyroid cancer, malignant melanoma, bladder cancer, and yolk sac tumor (site unspecified). The case of malignant melanoma reported previous history of melanocytic nevus, which started to change in character after etanercept therapy.

The FDA is evaluating the significance of these, as well as cases of lymphoma and malignancies reported with other anti-TNF agents. However, because of long latency, there may be a significant time lag between the use of product and development of and reporting of malignancies. Also, current etanercept usage estimates in children appear to be fairly small; thus, the risk of malignancies in pediatric population may potentially increase over time if overall exposure (including duration of exposure) in children increases in the future.

4. Given the waxing and waning nature of psoriasis, is sufficient information provided to inform physicians about how and when to initiate and discontinue therapy?

A practical consideration for use of etanercept for treatment of plaque psoriasis is how to advise physicians when to discontinue treatment and what would be the achievable efficacy upon restarting treatment. Patients and their parents would likely benefit from an understanding of the long-term consequences of initiating Enbrel therapy.

VII. Overall Benefit-Risk Assessment for Pediatric Patients

The committee will be asked to evaluate and summarize the benefits and risks associated with treatment of pediatric plaque psoriasis. Plaque psoriasis is not a life-threatening disease in childhood and complications are rare and largely psychosocial. Etanercept treatment is associated with life-threatening toxicities such as sepsis, anaphylaxis, and significant long-term morbidities such as malignancy, congestive heart failure, and demyelinating disease.

Given that the drug usage in the pediatric population is estimated to be fairly small at this time, the numbers and types of post-marketing adverse events reported are concerning. Many of these events, especially infection-related complications such as sepsis, were life-threatening and resulted in deaths and hospitalizations. Long-term potential toxicities such as malignancies and neurologic events are especially worrisome in children with plaque psoriasis who could receive chronic etanercept therapy. Given these considerable risks associated with etanercept, the benefit of this therapy in children with plaque psoriasis would need to be substantial in order to justify its approval and usage in the pediatric plaque psoriasis population.

The Committee will be asked for recommendations regarding whether pediatric plaque psoriasis populations treated with etanercept have been adequately studied to provide sufficient information on safety and efficacy to warrant Agency approval for this indication.

VIII. References:

Benoit, S and Hamm, H, Childhood Psoriasis. *Clin Dermatol*, 2007; 25: 555-562.

Gelfand, JM, Weinstein, R, Porter, SB, Neimann, AL, Berlin, JA, and Margolis, DJ, Prevalence and Treatment of Psoriasis in the United Kingdom, A Population Based Study. *Arch Dermatol*, 2005; 141: 1537-1541.

Lewkowicz, D and Gottlieb, AB, Pediatric Psoriasis and Psoriatic Arthritis, *Dermatologic Therapy*, 2004; 17: 364-375.

Paller, AS, and Mancini, AJ, eds. Childhood Psoriasis. In: Hurwitz Clinical Pediatric Dermatology, A Textbook of Skin Disorders of Childhood and Adolescence. Philadelphia: Elsevier Saunders; 2006: pp. 85-94.

Appendix

PASI Scoring per Appendix from Study Protocol

Appendix E. Psoriasis Area & Severity Index (PASI) Assessment

Psoriatic Involvement

Body Areas (corresponding to total body area)	Area of Involvement (numerical value 0-6)
Head (h) (10%)	
Trunk (t) (30%)	
Upper Extremities (u) (20%)	
Lower Extremities (l) (40%)	

Psoriatic Involvement (6 point scale)

0 = no involvement

1 = < 10% involvement

2 = 10 to < 30% involvement

3 = 30 to < 50% involvement

4 = 50 to < 70% involvement

5 = 70 to < 90% involvement

6 = 90 to 100% involvement

Severity of Psoriatic Lesions

	Head	Trunk	Upper Extremities	Lower Extremities
Erythema				
Infiltration				
Desquamation				

Severity of Psoriatic Lesions (4 point scale): assessed based on three target symptoms: *erythema* (E), *infiltration* (I) and *desquamation* (D).

0 = no symptoms present

1 = slight symptoms

2 = moderate symptoms

3 = striking symptoms

4 = exceptionally striking symptoms

Calculating the PASI:

$$\text{PASI} = 0.1 (E_h + I_h + D_h) A_h + 0.3 (E_t + I_t + D_t) A_t + 0.2 (E_u + I_u + D_u) A_u + 0.4 (E_l + I_l + D_l) A_l$$

[head]
[trunk]
[upper extremities]
[lower extremities]

The PASI varies in steps of 0.1 units from 0.0 to 72.0. The last figure thus represents complete erythroderma of the severest possible degree, while 0.0 means no psoriatic lesions at all.

Fredriksson T, Petersson U. Severe psoriasis – oral therapy with a new retinoid. *Dermatologica* 1978;157:238-244.

The attached documents are **CLEARED for the following purposes ONLY**. This coversheet must accompany all final documents that have been **CLEARED**.

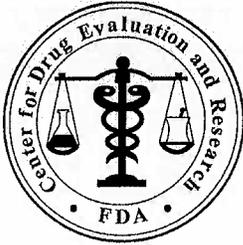
Audience:	Advisory Committee members and public
Purpose:	6/18/2008 Advisory Committee meeting
Date of Disclosure:	May 22, 2008
Data Vendors Used in Document:	IMS, Verispan

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: May 28, 2008

To: Susan Walker, M.D., F.A.A.D., Director
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Division of Anesthesia, Analgesia & Rheumatology Products

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Dave Moeny, R.Ph, DEPI

Subject: Post-Marketing Adverse Events in Pediatric Population, including
Cases with an outcome of death, Serious Domestic Events (Hospital,
Life-Threatening, and Congenital Anomaly), Malignancies, Varicella,
Macrophage Activation Syndrome, and Tuberculosis –
DODAC June 18, 2008 Version

Drug Name(s): Etanercept (Enbrel®)

Submission Number: 5350

Application Type/Number: BLA 103795

Applicant/sponsor: Amgen

OSE RCM #: 2007-2125

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EXECUTIVE SUMMARY

Amgen, the manufacturer of etanercept, has submitted a labeling supplement to the FDA seeking approval for treatment of moderate to severe psoriasis in children aged 4 to 17 years old. As part of the review process, the FDA is presenting efficacy and safety information concerning etanercept in pediatric patients at the Dermatologic and Ophthalmic Drugs Advisory Committee (AC) meeting on June 18, 2008. In preparation for the AC, the Office of Surveillance and Epidemiology's (OSE) Division of Adverse Event Analysis I (DAEA I) has been asked to review post-marketing adverse event reports of etanercept submitted for pediatric patients to re-examine known, and to identify potentially unknown safety issues. We also provide drug utilization information in this review. For the purpose of this review, the pediatric population is defined as children aged 4 to 17 years old.

DAEA reviewed all post-marketing pediatric cases retrieved from the Adverse Event Reporting System (AERS) with an outcome of death; and the majority (8 of 14 cases) occurred in patients who received etanercept for Juvenile Idiopathic Arthritis (JIA), which is the only approved indication for pediatric patients at this time. The most commonly reported cause of death was due to infectious complications. In addition, our review of serious domestic safety events in pediatric patients also showed that infections were the most commonly reported events that resulted in other serious outcomes, including hospitalizations and/or life-threatening outcomes (n=31).

Our review of domestic pediatric cases with serious outcomes showed that aside from infections, other commonly reported serious events were neurologic (n=10), gastrointestinal/hepatobiliary (n=9), musculoskeletal (n=8), and hematologic (n=6) events. Serious hematologic events of concern such as aplastic anemia and pancytopenia were reported; these events are labeled under Warnings section. There were 12 miscellaneous reports, which included other significant adverse events such as diabetes mellitus (n=3), systemic lupus erythematosus (n=2), and hypersensitivity reactions (n=2). One case of diabetes reported recurrence of diabetic ketoacidosis with reintroduction of etanercept therapy. Overall, most of these were qualitatively similar to adverse events already reflected in the etanercept labeling.

Nine malignancies (US 5, Foreign 4) were reported in pediatric patients who received etanercept. Three of nine were lymphoma cases in JIA patients. Although lymphoma has been associated in adults who received anti-TNF therapy (including etanercept), lymphoma is not a known complication of JIA, and the occurrence of these pediatric cases along with cases reported with other anti-TNF agents have been brought to the Agency's attention. Currently, the Agency is evaluating the significance of these, as well as cases of lymphoma and malignancies reported with other anti-TNF agents, and OSE is conducting a comprehensive review of all post-marketing malignancy cases associated with all anti-TNF agents. However, because of long latency, there may be a significant time lag between the use of product and development and reporting of malignancies. Also, current etanercept usage estimate in children appear to be fairly small (section 3.9); thus, the risk of malignancies in pediatric population may potentially increase over time if overall exposure (including duration of exposure) in children increases in the future.

Macrophage activation syndrome (MAS) is a known complication of JIA, and triggers of MAS include viral infections (such as EBV), non-steroidal anti-inflammatory drugs (NSAIDs), sulfasalazine, and methotrexate (MTX) therapy.¹ All thirteen MAS cases reported with etanercept occurred in patients with JIA; and nine of thirteen MAS cases were confounded by either JIA flare or EBV/viral infection. In addition, nine of thirteen cases were confounded by

concomitant medications such as MTX, NSAIDS, and sulfasalazine. However, the concomitant medications appeared to have been chronic medications and the reported MAS events were temporally associated with etanercept therapy in all cases. In addition, as anti-TNF agents have been known to reactivate EBV², it is biologically plausible that etanercept may cause reactivation of EBV and precipitate MAS in some susceptible patients.

Based on our current review and previous review of post-marketing events in children³, adverse events observed in pediatric population were qualitatively similar to those observed in adult population; also, similar to adults, some of these events lead to serious outcomes including deaths and hospitalizations. The risks associated with etanercept therapy in adult population are better known and multiple events have been evaluated, across multiple indications. Given the small exposure in pediatric population and small post-marketing safety data, especially in children with psoriasis, there is no evidence that the risk in children is different from those observed in adults, where significant safety concerns exist. This should be considered as we assess the overall benefit/risk for the proposed pediatric psoriasis indication for etanercept.

DAEA Recommendations

Our post-marketing review demonstrated that etanercept therapy was associated with serious adverse events in pediatric population such as infections and malignancies, similar to adults. Given that the drug usage in pediatric population is estimated to be fairly small at this time, the numbers and types of post-marketing adverse events reported are concerning. Many of these events, especially infection-related complications such as sepsis, were life-threatening and resulted in deaths and hospitalizations. Long-term potential toxicities such as malignancies and neurologic events are especially worrisome in children with plaque psoriasis who will likely receive etanercept therapy chronically. Thus, given these considerable risks associated with etanercept, the benefit of this therapy in children with plaque psoriasis would need to be substantial in order to justify its approval and usage in the pediatric plaque psoriasis population.

Following labeling changes are recommended regardless of pediatric psoriasis application outcome:

- The current etanercept labeling describes adverse events observed in the pediatric population under the '*Adverse Reactions in Patients with JIA*', and the labeling states that "the types of infections reported in JIA patients were generally mild and consistent with those commonly seen in outpatient pediatric populations". DAEA recommends enhancing the labeling to reflect that etanercept therapy in pediatric patients may lead to moderate to severe infections and can result in serious outcomes, including deaths and hospitalizations.
- DAEA recommends updating the serious adverse events reported in pediatric patients in post-marketing experience under the '*Adverse Reactions in Patients with JIA*' section with the following adverse events: macrophage activation syndrome, malignancies, diabetes mellitus, and systemic lupus erythematosus.
- A medication guide as previously recommended by OSE on March 27, 2007 review.

1 BACKGROUND

1.1 INTRODUCTION AND SCOPE OF REVIEW

Amgen, the manufacturer of etanercept, has submitted a labeling supplement to the FDA seeking approval for treatment of moderate to severe psoriasis in children aged 4 to 17 years old. As part of the review process, the FDA is presenting efficacy and safety information concerning etanercept in pediatric patients at the Dermatologic and Ophthalmic Drugs Advisory Committee (AC) meeting on June 18, 2008. In preparation for the AC, the Office of Surveillance and Epidemiology's (OSE) Division of Adverse Event Analysis I (DAEA I) has been asked to review post-marketing adverse events of etanercept reported in the pediatric population to re-examine known, and to identify potentially unknown safety issues. For the purpose of this review, the pediatric population is defined as children aged 4 to 17 years old, which is the age group studied for the pediatric psoriasis indication.

DAEA review provides a summary of all AERS pediatric adverse events and AERS pediatric adverse events with psoriasis indication reported with etanercept, in order to provide an overview of AERS cases. We selected to review all pediatric AERS cases with an outcome of death, as well as cases of malignancies, varicella, macrophage activation syndrome, and tuberculosis. Malignancies and tuberculosis are known safety issues with etanercept, and were reviewed to re-examine these risks in pediatric population. All post-marketing reports of varicella were reviewed, as cases of reactivated varicella were reported during clinical trial of pediatric psoriasis. Macrophage activation syndrome is an unlabeled event of interest identified in a previous pediatric review of anti-TNF agents, including etanercept³. In addition, the previous pediatric review of anti-TNF agents included an overview of serious domestic pediatric events³, and we provide an updated review of *serious domestic* pediatric events for etanercept.

Additionally, DEPI provides drug utilization data, stratified by age.

1.2 REGULATORY HISTORY

Etanercept is a tumor necrosis factor (TNF) receptor inhibitor produced by recombinant DNA in a Chinese hamster ovary mammalian cell expression system. Etanercept is a dimeric fusion protein composed of the extracellular ligand-binding portion of the human 75 kilodalton TNF receptor linked to the Fc portion of human IgG1. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels play an important role in both the pathologic inflammation and the joint destruction that occurs in patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis.

The approval history and approved indications for etanercept are listed in Table 1:

Table 1: Etanercept (Enbrel®) FDA Approved Indications and Dates of Approval

Date	FDA Approved Indication(s)
November 2, 1998	<ul style="list-style-type: none">To reduce the signs and symptoms of moderately to severely active rheumatoid arthritis in patients who have an inadequate response to one or more disease-modifying anti-rheumatic (DMAR) drugs.In combination with methotrexate in patients who do not respond adequately to methotrexate alone.
May 27, 1999	Polyarticular course juvenile rheumatoid arthritis (JRA) in patients 2 years old and

Date	FDA Approved Indication(s)
	older
June 6, 2000	Reducing the signs and symptoms and delaying structural damage in patients with moderately to severely active rheumatoid arthritis , including those who have not previously failed treatment with a disease-modifying anti-rheumatic drug.
January 15, 2002	Reducing signs and symptoms of active arthritis in patients with psoriatic arthritis .
July 24, 2003	Reducing signs and symptoms in patients with active ankylosing spondylitis .
July 24, 2003	Expand rheumatoid arthritis indication to include improving physical function.
August 21, 2003	Expand the indication to include inhibiting the progression of structural damage of active arthritis in patients with psoriatic arthritis .
April 30, 2004*	Treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy has been approved.

* Drugs@FDA: Enbrel, April 30, 2004, Post-Marketing Surveillance Letter for Psoriasis, BL 103795/5149 – Phase IV Safety Efficacy study in adult psoriasis patients.

1.3 PREVIOUS OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY (OSE) REVIEWS

As an anti-TNF agent, etanercept has been the subject of multiple OSE class reviews of adverse events associated with all anti-TNFs, etanercept, adalimumab and infliximab. The majority of these OSE post-marketing analyses were conducted for patients, irrespective of age who received an anti-TNF product. However, a review performed on May 9, 2006 (OSE PID# D050626) was conducted specifically on AERS data submitted for pediatric patients, aged 16 years old and younger. Specifically, the review information for etanercept described 69 domestic serious pediatric cases in patients 16 years old and younger, including one case each of tuberculosis and lymphoma, and cases of serious infection.

The subject of additional safety analyses conducted for the anti-TNF agents, including etanercept include:

- Sample of Death Reports for the anti-TNF agents, with attention to infections, malignancies and cardiac events
- Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
- Domestic Tuberculosis Cases
- AERS Crude Count and Datamining review
- Death cases associated with anti-TNF agents in patients with psoriasis or psoriatic arthritis
- Hepatitis B virus reactivation
- Guillain Barre Syndrome
- Malignancies
- Hepatotoxicity
- Pregnancy Outcomes

Additionally, on October 25, 2006, OSE reviewed the 'Post-Marketing Phase 4 Safety Surveillance Registry of Enbrel for Treatment of Psoriasis (Protocol 20040210)' submitted by Amgen to fulfill an approval commitment. This study was in adult psoriasis patients, and its objective was to assess the efficacy and safety of etanercept 50mg twice weekly for periods beyond 12 weeks. The study was a prospective, multi-center, active surveillance study of 2,500

adults patients with chronic plaque psoriasis treated with etanercept (Enbrel). The OSE reviewer made recommendations to compensate for what she determined to be study limitations, including the absence of controls, and the limited (2,500) sample size.

1.4 PRODUCT LABELING

The following adverse event information is found in the identified sections of the ENBREL® labeling. This information is excerpted information, is not all inclusive, and not all sections of the label are represented. Additional safety information can be found in the product label approved March 2008.

Boxed Warning (added March 2008)

- Infections, including serious infections leading to hospitalization or death, have been observed in patients treated with ENBREL® (see **WARNINGS** and **ADVERSE REACTIONS**).
- Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation) has been observed in patients... including ENBREL®.

Warnings

- Serious infections (including sepsis and tuberculosis), neurological events (including demyelinating disorders), hematologic events (including pancytopenia), malignancies (including lymphoma), hepatitis B virus reactivation

Adverse Reactions in Patients with Juvenile Idiopathic Arthritis (JIA)

- In general, the adverse events in pediatric patients were similar in frequency and type as those seen in adult patients. Differences from adults and other special considerations are further discussed in additional paragraphs in the label under this section heading. ... The types of infections reported in JIA patients were generally mild and consistent with those commonly seen in outpatient pediatric populations. Two JIA patients developed varicella infection and signs and symptoms of aseptic meningitis which resolved without sequelae.

Precautions

- Most psoriatic arthritis patients were able to mount effective B-cell immune responses to pneumococcal polysaccharide vaccine, but titers in aggregate were moderately lower... The clinical significance of this is unknown. Patients with significant exposure to varicella virus should temporarily discontinue ENBREL® therapy and be considered for prophylactic treatment with varicella zoster immune globulin.

Pediatric Use

- The safety and efficacy of ENBREL® in pediatric patients with plaque psoriasis have not been studied.

Adverse Reactions

- Injection site reactions, infections, malignancies, antibody formation, autoantibody formation, angioedema, non-infectious hepatitis, heart failure, worsening psoriasis.

Adverse Reaction Information from Spontaneous Reports

- Autoimmune hepatitis, lupus-like syndrome with manifestations including rash consistent with subacute or discoid lupus, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis

2 METHODS AND MATERIALS

DAEA queried the AERS database to identify post-marketing reports submitted for etanercept for patients aged 4 to 17 years old. Additionally, DEPI obtained drug use data.

2.1 AERS SELECTION OF CASES

All searches were conducted on April 14, 2008. We conducted separate searches of the AERS database to identify post-marketing adverse event reports submitted for etanercept as a suspect in the pediatric population aged 4 to 17 years old. We employed the following search terms and levels:

1. All reports submitted for etanercept as a 'suspect' for pediatric patients since marketing. We employed the trade name 'Enbrel', the active ingredient name 'Etanercept', and verbatim names associated with Enbrel and etanercept. We additionally employed the Advance Miscellaneous Criteria function of AERS and searched for all reports aged '4 to 17' years old.
2. All reports submitted for etanercept for pediatric patients with an indication of psoriasis. We employed the 'Advance Product Criteria' function of AERS and searched the 'Indication' field, under the MedDRA coded indication of 'Psoriatic Conditions' at the High Level Term (HLT), which includes the Preferred Terms of psoriatic arthropathy, dermatitis psoriasiform, erythrodermic psoriasis, guttate psoriasis, psoriasis, pustular psoriasis and nail psoriasis.
3. All reports submitted for etanercept for pediatric patients with an outcome of death. We employed the Advance Miscellaneous Criteria function of AERS and searched for all reports with an outcome of 'death'. There were 32 reports, of which 18 were excluded for following reasons:
 - Duplicates (n=12)
 - Patient received etanercept previously, and the event occurred shortly after infliximab therapy, with temporal relationship suggesting relationship with infliximab, not etanercept (n=3)
 - Reported event had stronger temporal relationship with anakinra and/or cyclophosphamide therapy; patient was on multiple immunosuppressants including MTX, azathioprine, corticosteroids, and etanercept, which were chronic medications for treatment of diffuse vasculitis (n=1)
 - No adverse event was reported (n=1)
 - Death was not an outcome; however, this case was included in domestic serious case series as patient was hospitalized (n=1)

The resulting 14 cases are summarized in section 3.2.

4. All reports of *serious domestic* cases submitted for etanercept for pediatric patients, where we selected 'domestic' and serious outcomes of 'hospitalization, life-threatening, and congenital anomaly' in the Advanced Miscellaneous Criteria function of AERS. There were 110 reports, of which 34 were excluded for following reasons:
 - Duplicates (n=11)
 - Reports reviewed for macrophage activation syndrome case series (n=6)
 - Foreign reports (n=4)
 - No adverse event reported (n=4)
 - Reported event related to other therapy (n=3)
 - Reports reviewed for varicella case series (n=3)
 - Report reviewed for malignancies case series (n=1)
 - The patient was an adult (n=1)
 - Patient did not receive etanercept (n=1)

Of resulting 76 cases, 48 cases were summarized in the previous OSE review³ and 28 cases were new cases since then. We combined the information of cases from the previous review with the new cases and summarized in section 3.3.

5. All reports of malignancies submitted for etanercept for pediatric patients. We employed 'Neoplasms benign, malignant and unspecified [incl cysts and polyps] (SOC)' MedDRA reaction term. There were 35 reports, of which 31 were excluded for following reasons:
 - Reports of macrophage activation syndrome; these cases are summarized separately from malignancies (n=11)
 - Duplicates (n=7)
 - No malignancies reported (n=7)
 - Reported event as a cyst or benign tumor (n=4)
 - Reports with pre-existing malignancy [leukemia, renal cell carcinoma] that relapsed (n=2)

In addition, since we anticipate that malignancies can be reported several years after initiating therapy, we expanded our age criteria up to 22 years and re-ran the search to capture all those who may have started etanercept when s/he was a pediatric patient, but was diagnosed with a malignancy as an adult. Through this search, we identified three additional cases of malignancies in patients who received etanercept as a pediatric patient and experienced malignancy as an adult.

The resulting 7 cases are summarized in section 3.4.

6. All reports of macrophage activation syndrome submitted for etanercept for pediatric patients. We employed 'Histiocytosis Hematophagic (PT)' and 'Macrophage Activation (PT)' MedDRA reaction terms. There were 22 reports, of which 13 were excluded for following reasons:
 - Duplicates (n=8)
 - Macrophage activation syndrome (MAS) occurred more than a month after etanercept discontinuation (n=2)
 - Reported MAS related to other therapy (n=1)
 - MAS not a definite diagnosis (n=1)
 - Reported event not MAS (n=1)

The resulting 9 cases are summarized in section 3.5.

7. All reports of varicella submitted for etanercept for pediatric patients. We employed 'Herpes Viral Infections (HLT)' MedDRA reaction term. There were 11 reports, of which one case of herpes simplex case was excluded. The resulting 10 cases are summarized in section 3.6.
8. All reports of tuberculosis submitted for etanercept for pediatric patients. We employed 'Tuberculosis Infections (HLT)' MedDRA reaction term. There were 5 reports, of which 3 were excluded for following reasons:
 - Duplicates (n=2)
 - Tuberculosis related to infliximab, not etanercept (n=1)

The resulting 2 cases are summarized in section 3.7.

2.2 ADDITIONAL CASES FROM THE SPONSOR

On May 1, 2008, we requested the sponsor to submit copies of all pediatric cases (both serious and non-serious) under Neoplasm SOC. We identified two additional cases of malignancy and four additional cases of macrophage activation syndrome from the sponsor's submission, and these have been included in the result of malignancy cases in section 3.3 and macrophage activation syndrome in section 3.4, respectively.

2.3 DRUG UTILIZATION DATA

2.3.1 Determining setting of care

IMS Health, IMS National Sales Perspectives™ data were used to determine the primary settings in which etanercept is sold. Nationally projected sales of etanercept by number of vials from the manufacturers into the various retail and non-retail channels of distribution were analyzed for four calendar years from 2004 through 2007.⁴ The proportion of sales to mail order pharmacies rose from 43% in 2004 to 56% during 2007 while sales to retail pharmacies declined from 47% during 2004 to 34% during 2007. Sales to non-retail pharmacies remained constant during the analysis period accounting for 10-11% of sales during each year examined.

Because most of the product sold during this time period went to outpatient pharmacies (retail and mail-order), we examined utilization patterns focusing on the outpatient setting. Sales data indicate that the Verispan database VONA is the most appropriate data source to measure the use of these products among the databases licensed by FDA.

2.3.2 Data sources used

We examined wholesale sales data using IMS Health's IMS National Sales Perspectives. Outpatient use was measured with two data sources from Verispan, LLC: Vector One®: National (VONA), and Total Patient Tracker (TPT). Using the VONA database we obtained nationally projected prescription counts stratified by patient age and by physician specialty for the years 2002-2007. Using TPT, we obtained projected counts of the number of unique patients receiving a prescription (stratified by age) for the years 2002-2007. Finally, we obtained age stratified data for the diagnoses which were associated a mention of etanercept by office based physicians (indications for use) using the Verispan, Physician Drug and Diagnosis Audit (PDDA) for the years 2002-2007. Complete descriptions of the databases used are provided in Appendix 2.

3 RESULTS

3.1 OVERVIEW OF PEDIATRIC ADVERSE EVENTS

3.1.1 CRUDE COUNTS AERS REPORTS IN CHILDREN AGED 4 TO 17 YEARS OLD (N = 949)

Of 54,710 total etanercept post-marketing reports in the AERS database, we identified 949 reports submitted for children aged 4 to 17 years old who were exposed to etanercept as a primary suspect agent. The reports returned from this search represent crude numbers; duplicated cases have not been reconciled, and individual cases have not been assessed for causality. Seventy-five percent of the reports were domestic reports submitted for children with a median age of 13 years old, with a range of 4 to 17 years. There were more females (71%) reporting adverse events than males (27%). The outcomes in these reports are categorized as unique outcomes, and are

reported as non-overlapping, although a report may have reported multiple outcomes. As such the categorized outcomes include 32 deaths (representing 14 unique cases that are further described in section 3.2 below), 200 hospitalizations, and six life-threatening outcomes.

Additionally, the AERS database contains an indication field, and in the 882 reports that provided information, arthritis and arthritis related indications and other labeled indications were primarily described. These reports were not subjected to a hands-on review, but some of the cases potentially described what can be considered as off-labeled use. The listing of the potential indications is provided in Table 2 below.

Table 2: Overall Characteristics of Etanercept AERS Crude Count Adverse Event Reports in Children aged 4 to 17 years old from Marketing to April 14, 2008, n = 949

Location	US (711), Foreign (219), Not Reported (19)
Gender	Female (677), Male (254), Not Reported (18)
Age	Range 4 to 17 years old, median = 13 years, n = 949
Report years	1999 (49), 2000 (64), 2001 (72), 2002 (37), 2003 (40), 2004 (43), 2005 (68), 2006 (210), 2007 (328), 2008* (35)
Outcome	Death (32- representing 14 unique cases when duplicates are reconciled), Hosp (200), Life-threatening (6), Required Intervention (3). Other and Non-Serious (708)
Indication of use** (n =882)	Anal fistula (1), Ankylosing Spondylitis (26), Aplastic Anemia (1), Arthritis (7), Arthropathy (1), Asthma (1), Bechet's Syndrome (3), Idiopathic Pneumonia Syndrome (6), Chronic Arthritis (1), Crohn's Disease (1), Cinca Syndrome (1), Dermatomyositis (3), Diffuse Vasculitis (1), NR (65), Erosive Arthritis (1), Familial Mediterranean/periodic Fever Syndrome (2), GVHD (6), Idiopathic Thrombocytopenia (1), Iridocyclitis (1), JRA (592), Mixed Connective Tissue Disease (1), Nerve Injury (1), Overlap Syndrome (1), Parophthalmia (1), Polyarthritis (15), Polymyositis (1), Psoriasis (61), Psoriatic Arthropathy/Arthritis (47), Rheumatoid Arthritis (71), Sarcoidosis (3), Spondylitis/Spondyloarthropathy (10), Stills Disease (2), Takayasu's Arteritis (1), Uveitis (6), Vasculitis (2), Wegener's Granulomatosis (2)
Report Type	Direct (28); Expedited 15 Day (368); Periodic (553)

* Partial year

**These reports have not been reviewed – this is the indication listed in the indication field of the MedWatch form.

3.1.2 MOST FREQUENTLY REPORTED ADVERSE EVENTS IN CHILDREN AGED 4 TO 17 YEARS OLD TREATED WITH ETANERCEPT FROM MARKETING TO APRIL 14, 2008 (CRUDE COUNTS)

The following table lists the 20 most commonly reported adverse event terms reported for etanercept in children aged 4 to 17 years old. A similar table for adalimumab and infliximab is found in appendix 5. Please note that these are crude counts of the reports, and a report may contain multiple terms. Additionally, duplicated reports have not been reconciled, nor has causality been assessed.

Nearly all (18 of 20) of the commonly reported adverse event terms (e.g. injection site reactions, headaches, upper respiratory infections, etc.) are described in current labeling, except for two terms (Juvenile and Rheumatoid arthritis) which are indications for use of the product.

The most commonly reported adverse events in the pediatric population are very similar to those reported in all ages exposed to etanercept (see appendix 4). In children, of the labeled adverse events that were commonly reported, there were also labeled adverse events of known concern that were not as commonly reported. These included events such as serious infections (including

TB), serious skin reactions (such as Steven Johnsons Syndrome), malignancy and neurological adverse events.

Table 3: Crude Counts of Most Commonly Reported AERS Adverse Event Terms for Etanercept in Children Aged 4 to 17 years old, from Marketing to April 14, 2008

Rank	Adverse Event Term	# of Reports
1	Injection Site Pain (labeled)	102
2	Injection Site Reaction (labeled)	85
3	Condition Aggravated (some clinical event worsening described in label)	73
4	Pyrexia (labeled as fever)	63
5	Headache (labeled)	49
6	Injection Site Bruising (labeled)	38
7	Juvenile Arthritis (indication)	36
8	Vomiting (labeled)	34
9	Arthralgia (labeled joint pain)	30
10	Nausea (labeled)	29
11	Injection Site Erythema (labeled)	28
12	Uveitis (labeled as ocular inflammation)	25
13	Injection Site Pruritis (labeled)	24
14	Pain (labeled)	22
15	Abdominal Pain (labeled)	21
16	Cough (labeled)	20
17	Drug Ineffective (not applicable)	20
18	Injection Site Irritation (labeled)	20
19	Rheumatoid Arthritis (indication)	20
20	Upper Respiratory Tract Infection (labeled)	19

3.2 CASES WITH AN OUTCOME OF DEATH

Table 4: Characteristics of Etanercept Pediatric AERS Cases, Ages 4 to 17 years, with an Outcome of Death, US and Foreign Cases from Marketing to April 14, 2008 (N=14)

Age distribution	Range - 4 to 17 years Median - 9.5 years
Gender	Male - 8 Female - 6
Indication	JIA - 8 IPS - 3 GVHD - 2 Unknown - 1
Time to onset (n=11)	Range - 1 day to 34 months Median - 1 month
Relevant co-suspect/concomitant immunosuppressants (n=9)	<ul style="list-style-type: none"> • MTX, corticosteroid - 4 (reported as co-suspects in 2) • MTX - 1 • Basiliximab, cyclosporine, corticosteroid - 1 (basiliximab as co-suspect) • Busulfan, cyclosporine, cytarabine, corticosteroid - 1

	(busulfan, cyclosporine, cytarabine were co-suspects) <ul style="list-style-type: none"> • Corticosteroid, cyclosporine - 1 (corticosteroid as co-suspect) • MTX, tacrolimus - 1
Reported dose (n=9)	Range - 0.3 mg/kg - 0.8 mg/kg Median - 0.4 mg/kg
Report type	Expedited (15-day) - 13 Direct - 1
Reporter	Physician - 10 Health care professional - 2 Pharmacist - 1 Lawyer - 1
Source	US - 7 (2 study reports & 1 reported in literature ⁵) Foreign - 7

Abbreviations; JIA=juvenile idiopathic arthritis, IPS=idiopathic pulmonary syndrome, GVHD=graft-versus-host-disease, MTX= methotrexate

Eight of fourteen cases received etanercept for treatment of JIA. All of these eight cases were also on concomitant or co-suspect medications such as methotrexate and/or corticosteroid. The causes of death reported included infections (n=4), cardiac (n=1), liver failure (n=1), immunodeficiency (n=1), and unknown (n=1):

- The four cases of deaths due to infection included three cases of sepsis (one also experienced bronchopneumonia) and one case of pneumococcal meningitis. The time to onset reported in three cases ranged from 4 months to 34 months (one unknown). The pathogens responsible for sepsis were not reported, but one was reported to be due to an unspecified bacteria.
- One case reported experiencing cardiorespiratory arrest after being hospitalized for dyspnea, with cause of death thought to be due to cardiac failure. His past medical history was significant and included Kawasaki's syndrome, cardiac murmur, and tachycardia.
- One case experienced liver failure four to five weeks after starting etanercept and subsequently died on an unknown date. She had a history of Kawasaki's disease and also received methotrexate concomitantly.
- One case reported arthritis flare-up and lower respiratory tract infection after etanercept therapy, and he subsequently died after another episode of arthritis flare-up; the cause of death was reported as immunodeficiency.
- One foreign case reported fever, vomiting, and diarrhea after couple of hours of receiving the first dose of etanercept, and subsequently experienced cyanosis, hypotension, trembling, and loss of consciousness. He was not taken to the hospital due to distance, and died 20 hours later. The cause of death was unknown.

Five of fourteen cases had history of leukemia and received etanercept for treatment of graft-versus-host-disease (GVHD) or idiopathic pulmonary syndrome (IPS) following stem cell transplantation. Four of five patients reported concomitant or co-suspect immunosuppressants such as basiliximab, cyclosporine, busulfan, cytarabine, and/or corticosteroid. The reported causes of death were as following:

- One case reported experiencing CMV reactivation after etanercept therapy, but later died due to progressive hepatic failure from underlying hepatic veno-occlusive disease.

- Multi-organ failure, which was attributed to multiple causes including interstitial pneumonitis, renal failure, and CMV reactivation
- Multiorgan failure after experiencing renal failure and neurologic symptoms
- Aspergillosis infection
- Idiopathic pulmonary syndrome

In one remaining case with an unknown indication for etanercept use, the cause of death was pulmonary edema due to left ventricular failure after receiving etanercept for an unspecified time; the patient had a previous history of pulmonary edema.

3.3 SERIOUS DOMESTIC CASES

Overall characteristics of 48 cases summarized in the previous OSE review³ and 28 cases reported since then are combined and presented in Table 8:

Table 5: Characteristics of Etanercept Pediatric AERS Cases with Selected Serious Outcomes [Hospitalizations, Life-Threatening, Congenital Anomaly], US Cases from Marketing to April 14, 2008 (N=76)

Age distribution	Range - 4 to 17 years Median - 13 years
Gender	Female - 58 Male - 18
Indications	JIA - 54 Psoriasis and psoriatic arthritis - 4 Psoriasis - 3 Rheumatoid arthritis - 2 Spondyloarhtropathy - 2 Psoriatic arthritis - 1 GVHD - 1 Idiopathic thrombocytopenia purpura (ITP) - 1 Familiar Periodic Fever Syndrome - 1 Ankylosing spondylitis - 1 Wegener's granulomatosis - 1 Unknown - 5
Time to onset (n=67)	Range - 1 day to 4 years Median - 6 months
Serious outcomes	Hospitalization - 74 (6 also considered to be life-threatening) Life-threatening - 2
Adverse Events Category	Infections - 31 Neurologic Events - 10 Gastrointestinal/hepatobiliary events - 9 Musculoskeletal Events - 8 Hematologic Events - 6 Other/miscellaneous - 12
Reported dose (n=30)	Range - 0.2 - 0.8 mg/kg Median - 0.4 mg/kg
Report type	Expedited (15-day) - 52 Periodic - 17 Direct - 7
Reporter	Health care professional - 61: <ul style="list-style-type: none"> • Physician - 52 • Pharmacist - 5 • Unspecified health care professional - 2

	<ul style="list-style-type: none"> • Research coordinator - 1 • Physician Assistant - 1 Consumer - 15
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INFECTIONS (N=31)

Thirty-one pediatric cases who received etanercept reported serious infections, where the types of infection and reported pathogens identified were as following:

- 5 respiratory tract infections (3 pneumonia, 2 unspecified)
- 4 abscesses (1 methicillin-resistant *Staph aureus* septic abscess⁶)
- 4 urinary tract infections (1 *E. coli*)
- 3 sepsis/septic shock (1 beta-hemolytic streptococci, 1 *listeria*; one case of septic shock occurred with pneumonia)
- 2 osteomyelitis (one due to *Staph aureus*)
- 2 cellulitis
- 2 ear infections
- 1 conjunctivitis
- 1 flu syndrome
- 1 sinusitis (also experienced trigeminal neuralgia, possibly due to infection)
- 1 systemic histoplasmosis
- 1 streptococcal throat infection
- 1 Staphylococcal toxic shock syndrome
- 3 unspecified infections (one case each of streptococcus, unspecified bacterial, and unspecified viral infection)

The overall characteristics of these 31 cases of infections are summarized in Table 6:

Table 6: Characteristics of Etanercept Pediatric AERS Cases of Infections with Selected Serious Outcome [Hospitalization, Life-Threatening, Congenital Anomaly], US Cases from Marketing to April 14, 2008 (N=31)

Age distribution	Range - 4 to 17 years Median - 12 years
Gender	Female - 24 Male - 7
Indication	JIA - 24 Spondyarthropathy - 2 Psoriasis - 2 Psoriasis & Psoriatic arthritis - 1 Psoriatic arthritis - 1 Rheumatoid arthritis - 1
Time to onset (n=25)	Range - 1 day to 4 years Median - 8 months
Relevant co-suspect/concomitant immunosuppressants (n=22)	<ul style="list-style-type: none"> • MTX - 8 • MTX, corticosteroid - 5 (also co-suspects in 2) • Corticosteroid - 2 • Hydroxychloroquine - 2 • MTX, corticosteroid, hydroxychloroquine - 1 • MTX, corticosteroid, mycophenolate - 1 • MTX, corticosteroid, cyclosporine - 1 • MTX, azathioprine - 1 • Azathioprine, cyclosporine, hydroxychloroquine, corticosteroid - 1
Reported dose (n=20)	Range - 8 mg twice weekly to 50 mg once weekly,

	with 0.2 to 0.66 mg/kg per dose Median - 25 mg twice weekly (0.4 mg/kg per dose)
Report type	Expedited (15-day) - 16 Periodic - 13 Direct - 2
Reporter	Physician - 18 Pharmacist - 2 Healthcare professional - 2 Physician Assistant - 1 Consumer - 8

Several predisposing factors and/or significant previous history for reported infectious complications included the following:

- A case of systemic histoplasmosis reported travel to rural Poland two months before the event.
- A case with methicillin-resistant *Staph aureus* septic abscess reported insect bite at the site of infection
- A case with an unknown lung infection has cystic fibrosis.
- A case of urinary tract infection (UTI) has previous history of UTIs; however, none had required hospitalizations.
- A case of pneumonia and septic shock 36 hours after the first dose of etanercept had recently received infliximab.

Thirteen of 31 cases reported improvement, where nine cases reported receiving antibiotics/antifungal therapy. There was one positive rechallenge case, where the peritonsillar abscess recurred three times after restarting etanercept. Four cases reported reintroduction of etanercept therapy, without further infectious complications at the time of report.

NEUROLOGIC EVENTS (N=10)

Ten reported serious neurologic events were as following:

- 5 seizures:
 - One case also experienced aphasia and weakness
 - One case reported history of epilepsy, and another case of seizure reported possible infectious cause (which was not confirmed)
- 2 pseudotumor cerebri:
 - One case also experienced optic neuritis
 - Another case experienced multiple neurologic events, including cerebral atrophy, cerebral venous thrombosis, aseptic meningitis, neurotoxicity, and pneumonitis
 - Both cases received concomitant corticosteroids, which have been associated with pseudotumor cerebri⁷
- 2 headaches (one was considered to be migraine headache)
 - One case reported history of chronic headache
- 1 multiple sclerosis with optic neuritis

The time to event onset ranged from 4 days to 4 years, with a median of 6.5 months. The indications included JIA (n=4), ankylosing spondylitis (n=1), GVHD (n=1), psoriasis and psoriatic arthritis (n=1), familial periodic fever syndrome (n=1), uveitis (n=1), and unknown

(n=1). In six of ten cases, concomitant immunosuppressants were reported, which included methotrexate, corticosteroid, cyclosporine and/or hydroxychloroquine.

Six cases reported positive dechallenges, where the neurologic events resolved with discontinuation of etanercept (two patients received treatment). One positive rechallenge was reported in a patient who received etanercept for familial periodic fever syndrome, where aphasia recurred and seizure occurred upon re-introduction of etanercept.

GASTROINTESTINAL/HEPATOBIILIARY EVENTS (N=9)

Nine serious gastrointestinal/hepatobiliary events were as following:

- 2 related to appendix - one appendicitis and one case of ruptured appendix, both required appendectomy
- 1 vomiting and dehydration
- 1 colitis
- 1 intestinal infarct/ischemia
- 1 jaundice, hepatomegaly
- 1 ulcerative colitis and liver failure [A 14 year-old JIA patient developed colitis after 2.5 years of etanercept therapy; past history included autoimmune thyroiditis (six years), steatohepatitis (three years), and previous therapy with infliximab and MTX; etanercept therapy was resumed few months later, and the patient developed liver failure within a month and was waiting for transplantation.]
- 1 gastrointestinal bleeding
- 1 anal fistula

The time to onset ranged from 28 days to 30 months, with a median of 1 year (n=7). The indications included JIA (n=8) and psoriasis (n=1). Three cases reported concomitant use of MTX and/or corticosteroid. Four cases reported improvement after discontinuation of etanercept.

MUSCULOSKELETAL EVENTS (N=8)

Eight serious musculoskeletal events included one case each of:

- JIA flare
- Worsening JIA
- Worsening JIA/exacerbation of psoriatic arthritis
- Tenosynovitis of right hand, wrist, ankle, and foot
- Left arm swelling
- Shoulder joint replacement
- Knee and hip replacement
- Epiphyses premature fusion (growth plate)

The time to onset ranged from 4 days to 3.6 years, with a median of 1 month (n=7). The indications included JIA (n=6), psoriatic arthritis/psoriasis (n=1), and unknown (n=1). All eight cases reported concomitant use of immunosuppressants, which included corticosteroids, MTX, hydroxychloroquine, and/or cyclosporine. In two cases, etanercept therapy continued; in another case of worsening JIA and psoriatic arthritis, the severity of symptoms continued to increase after stopping etanercept despite therapy with other immunosuppressants.

HEMATOLOGIC EVENTS (N=6)

Six serious hematologic events included one case each of:

- Aplastic anemia [A 16-year-old male patient started etanercept and MTX therapy for treatment of JIA. About a month later, a complete blood count revealed pancytopenia. A bone marrow biopsy showed hypocellular marrow, and he was diagnosed with aplastic anemia. The patient was undergoing a work-up for bone marrow transplant.]
- Pancytopenia, hemolytic anemia (also experienced ear infection, most likely due to neutropenia) [A 16-year-old female patient began etanercept therapy for treatment of JIA. She had a history of intermittent thrombocytopenic purpura, hemolytic anemia, and autoimmune neutropenia prior to etanercept. After several weeks of etanercept therapy, her dose was decreased after an episode of thrombocytopenia and leukopenia; few months later, etanercept therapy was briefly discontinued due to progressive pancytopenia. Six months after etanercept therapy, she was hospitalized with a hemolytic anemia and received high-dose corticosteroids; etanercept therapy was discontinued. Six months later, etanercept therapy was resumed, and nine months later etanercept was permanently discontinued due to pancytopenia.]
- Leukopenia, anemia
- Neutropenia
- Thrombocytopenia, petechiae
- Hemolysis, disseminated intravascular coagulopathy

The time to onset ranged from 2 weeks to 14 months, with a median of 2 months. Five patients received etanercept for JIA, and one patient for ITP. Five cases reported concomitant MTX, sulfasalazine, and/or azathioprine. The case of pancytopenia/hemolytic anemia reported previous history of intermittent thrombocytopenia and autoimmune neutropenia, but it was reported that the hematologic events had not been consistently problematic prior to starting etanercept. Three of six cases reported positive dechallenges; one case of aplastic anemia did not improve after stopping etanercept and was undergoing work-up for possible bone marrow transplant. Two cases, hemolysis/DIC and pancytopenia/hemolytic anemia, reported positive rechallenges.

OTHER (N=12)

Other serious events included following:

- **Three cases** of diabetes occurred in pediatric patients who received etanercept for JIA, with reported times to onset of 5 months, 18 months, and 2 years. Two of three cases were diagnosed with Type I diabetes mellitus (DM); one case was also reported in literature⁸. The remaining case reported 'pre-diabetes' and weight gain; this patient had a history of obesity. One DM case reported hospitalization due to recurrence of diabetic ketoacidosis with reintroduction of etanercept (positive rechallenge).
- **Two** hypersensitivity reactions occurred. A 16-year-old female received etanercept for psoriasis and experienced anaphylaxis. Another hypersensitivity reaction occurred in a 15-year-old female who received etanercept for psoriatic arthritis and was hospitalized with nausea, vomiting, fever, hypotension, and erythroderma after eighth etanercept injection; blood culture was positive for *Staph aureus*, etanercept

was discontinued, and the patient was treated with intravenous antibiotics and supportive therapy. On an unknown date, etanercept was restarted and the same symptoms recurred; patient was hospitalized in the intensive care unit, and the physician reported that the event initially thought to be sepsis is believed to be a hypersensitivity reaction related to etanercept.

- **Two** cases of lupus were reported. A 16-year-old female with history of positive antinuclear antibodies received etanercept for JIA and developed systemic lupus erythematosus (SLE) two years later. Another case occurred in a four-year-old girl one month after starting etanercept, who presented with a vasculitic rash on the face, arms, and legs, and vasculitis in the fingers; she was diagnosed with drug-induced SLE secondary to etanercept use. Both cases received treatment with corticosteroids and improved.
- **One** case of myasthenia gravis occurred in a 17-year-old male after receiving etanercept for nine months for JIA. The patient improved after thymectomy and pyridostigmine therapy.
- **One** case of painful purpuric lesions was reported in a patient who received etanercept for treatment of Wegener's granulomatosis. The patient had similar lesions before etanercept therapy, but never painful; the biopsy of the lesion was consistent with Wegener's granulomatosis.
- One case of GVHD in a patient who received etanercept for GVHD therapy.
- Two cases experienced multitude of symptoms without any specific diagnosis:
 - Musculoskeletal pain, chest pain, throat pain, and hypertension
 - Hypotension, tachycardia, swelling, vomiting, syncope, and fever

3.4 MALIGNANCIES

Overall characteristics of seven malignancies from AERS and two malignancies from the sponsor's submission are summarized in Table 7:

Table 7: Characteristics of Etanercept Pediatric AERS Cases of Malignancies, US and Foreign Cases from Marketing to April 14, 2008 (N=9)

Age distribution	Range - 10 to 18 years* Median - 17 years
Gender	Female - 4 Male - 4 Unknown - 1
Indication	JIA - 7 (+ psoriatic arthritis in one) Ankylosing spondylitis - 1 Unknown - 1
Time to onset (n=7)	Range - 29 days to 7 years Median - 2.5 years
Serious outcome due to malignancy	Hospitalization - 5 (+ life-threatening in one) Life-threatening - 2
Relevant co-suspect/concomitant immunosuppressants (n=6)	<ul style="list-style-type: none"> • Corticosteroid - 2 • MTX, corticosteroid - 2 (MTX co-suspect in one) • MTX - 1 (co-suspect) • MTX, azathioprine, corticosteroid - 1 (MTX &

	azathioprine were co-suspects)
Reported dose (n=5)	0.4 mg/kg - 1 25 mg - 4
Report type	Expedited (15-day) - 5 Periodic - 1 Direct - 1 From the sponsor submission - 2
Reporter	Physician - 6 Healthcare professional - 2 Consumer - 1
Source	US - 5 Foreign - 4 (3 registry reports)

*Three cases received etanercept when they were 17 years or younger & was diagnosed with malignancy when they were 18 years old.

The reported malignancies included one case each of Hodgkin's lymphoma, malignant lymphoma and acute myeloid leukemia (AML), diffuse B-cell non-Hodgkin's lymphoma (NHL), unspecified leukemia, myelodysplastic syndrome, papillary thyroid cancer, malignant melanoma, bladder cancer, and yolk sac tumor (site unspecified). The case of malignant melanoma reported previous history of melanocytic nevus, which started to change in character after etanercept therapy. The case of malignant lymphoma and AML reported history of smokeless tobacco use and family cancer.

The Hodgkin's lymphoma case reported remission after chemotherapy and discontinuation of etanercept. In the case of malignant lymphoma and AML, improvement was reported after chemotherapy; the case of malignant melanoma reported recovery after surgical excision. The patient with myelodysplastic syndrome reported recovery after receiving high-dose corticosteroid therapy; at the time of event, patient discontinued etanercept along with concomitant MTX and azathioprine. Subsequently, etanercept and methotrexate were re-introduced whereas azathioprine remains permanently discontinued (the outcome of rechallenge with etanercept was unknown). The case of diffuse B-cell NHL reported recovery about 3 months later. The patient with yolk-sac tumor eventually recovered after undergoing orchiectomy followed by chemotherapy. At the time of reporting, the event of papillary thyroid cancer was ongoing despite thyroidectomy and thyroid ablation therapy, and the event of leukemia was ongoing. The outcome in one case of bladder cancer was unknown.

3.5 MACROPHAGE ACTIVATION SYNDROME

Overall characteristics of nine cases from AERS and four cases from the sponsor's submission are summarized in Table 8:

Table 8: Characteristics of Etanercept Pediatric AERS Cases of Macrophage Activation Syndrome, US and Foreign Cases from Marketing to April 14, 2008 (N=13)

Age distribution	Range - 6 to 17 years Median - 11 years
Gender	Female - 10 Male - 3
Indication	JIA - 13, where 7 reported systemic JIA (+MAS in one case)
Time to onset (n=12)	Range - 2 weeks to 44 months Median - 16 months
Serious outcome due to MAS	Hospitalization - 11 (6 also life-threatening) Life-threatening - 1
Relevant co-suspect/concomitant	Indomethacin - 1 (co-suspect)

medications (n=9)	MTX, cyclosporine, corticosteroid (co-suspects) MTX, sulfasalazine, ketoprofen, indomethacin - 1 MTX, corticosteroid, naproxen - 1 Leflunomide, corticosteroid, indomethacin - 1 MTX, naproxen - 1 MTX, corticosteroid - 1 MTX - 1 Ibuprofen - 1
Reported dose (n=9)	0.4 mg/kg (5), 0.3 mg/kg, 12 mg, 25 mg, 50 mg
Report type	Expedited (15-day) - 9 From the sponsor submission - 4
Reporter	Physician - 9 Health care professional - 2 Investigator - 1 Unknown - 1
Source	US - 6 (3 reported in literature ^{9,10} & 2 were study reports) Foreign - 5 (3 reported in literature ¹¹⁻¹³ & 1 registry report) Unknown - 2 (both were study reports)

In two cases, MAS was not related to JIA flare, as arthritis symptoms improved with etanercept therapy. In both of these cases, the onset of MAS occurred two weeks after starting etanercept, whereas the time to onset was longer in all the other cases (8 - 44 months). In three other cases, MAS was preceded by JIA flare. The macrophage activation syndrome was related to EBV infection in four of thirteen cases. In addition, one other case reported concurrent viral infection, and another case reported concurrent pneumonia event and thought that it may have precipitated MAS. Nine of thirteen children received concomitant MTX, NSAIDs, and/or sulfasalazine, which have been reported as possible inciting factors for MAS.¹ Three cases reported previous history of MAS.

In eleven children, discontinuation of etanercept (and MTX in two children, indomethacin in one child) and treatment with intravenous corticosteroids, other immunosuppressants, and/or supportive therapy resulted in resolution of MAS. In four children, etanercept was restarted, and another occurrence of MAS with JIA was reported in one of these cases (the outcome of rechallenge was not provided in three remaining cases).

3.6 VARICELLA

Table 9: Characteristics of Etanercept Pediatric AERS Cases of Varicella, US and Foreign Cases from Marketing to April 14, 2008 (N=10)

Age distribution	Range - 5 to 16 years Median - 7.5 years
Gender	Female - 7 Male - 2 Unknown - 1
Indication	JIA - 8 Ankylosing spondylitis - 1 Vasculitis - 1
Time to onset (n=4)	Range - 3.5 months to 3 years Median - 16 months
Serious outcome due to varicella	Hospitalization - 6
Relevant co-suspect/concomitant immunosuppressants (n=5)	MTX - 3 MTX, steroid (reported as co-suspects) - 1 MTX, azathioprine, steroid - 1

Reported dose (n=7)	0.4 mg/kg (3), 0.75 mg/kg, 8 mg, 10 mg, 50 mg
Report type	Expedited (15-day) - 6 Periodic - 3 Direct - 1
Reporter	Physician - 5 Health care professional - 2 Consumer - 2 Research investigator - 1
Source	US - 6 (1 was a study report) Foreign - 4 (3 were registry reports)

Only one case reported source of exposure, where chickenpox occurred at the patient's school. In another case, there was no known exposure to varicella, and the final diagnosis was primary varicella infection that was community acquired. Two cases reported previous history of varicella infection. The source or history of varicella infection in the remaining six cases was not reported.

Five of ten cases reported improvement; four of five cases reported receiving oral or intravenous acyclovir treatment. The outcomes in the remaining five cases were not provided.

3.7 TUBERCULOSIS

Two foreign cases of tuberculosis in pediatric patients who received etanercept were reported:

AERS ISR#3888016, received 2002, foreign/literature¹⁴

A nine-year-old girl with systemic-onset JIA was started on etanercept therapy at 0.4 mg/kg as a substitute for methotrexate due to poor control of disease. Five weeks later, a painful swollen left ankle occurred, and clear synovial fluid aspirated from the joint isolated *M. tuberculosis*. Etanercept was discontinued, and antituberculosis therapy was initiated and extended for 12 months. She was restarted on methotrexate for control of her JIA, and is reportedly doing well 18 months later.

AERS ISR#5659807, received 2008, foreign

A 15-year-old received etanercept therapy for JIA at 25 mg twice weekly. Concomitant medications included methotrexate and naproxen. About 29 months later, she experienced pulmonary tuberculosis and was hospitalized. She was treated with unspecified antibiotic therapy, and the event was ongoing at the time of report.

3.8 ETANERCEPT REPORTS IN PEDIATRIC PSORIASIS PATIENTS (N=61)

The 61 reports in children with psoriasis treated with etanercept are a subset of the 949 reports that are described in section 3.1.1 above. The majority (59/61) of the reports in this subset were from the US, and were submitted primarily for female (44/61) children. The first two reports were submitted in 2003, followed by no reports in years 2004 and 2005. The year 2006 saw an uptick of reports (21), followed by a peak of 36 reports in 2007. So far in 2008 there have been two reports submitted in this population; however, drug use is also very low in this age group. Many of the commonly reported adverse event terms were labeled events and included injection site reaction related events. There were no death reports in this subgroup from marketing to the search date of April 14, 2008. The most serious outcomes reported included five hospitalizations, which are discussed later in this section; four of five hospitalized cases are also included in the summary of serious domestic cases (section 3.3).

Table 10: Pediatric Etanercept Psoriasis Post-Marketing Reports Submitted to the AERS database from Marketing to April 14, 2008

Location	US (59), Foreign (1), NR (1)
Gender	Male (16), Female (44), NR (1)
Age	4 to 17, median = 14 years,
Report years	2003 (2), 2006 (21), 2007 (36), 2008 (2)
Outcomes (unique cases)	Hosp (5), Required Intervention (1), Other/Serious/Non-Serious (55)
Adverse Events – commonly reported	Injection site pain (17), injection site reaction (8), injection site bruising (7), psoriasis (7), headache (6), condition aggravated (5), pyrexia (5), injection site irritation (4), abdominal pain (3), arthralgia (3), back pain (3), injection site swelling (3), sinusitis (3), alopecia (2), cough (2), dizziness (2), injection site erythema (2), injection site pruritis (2), nasopharyngitis (2), pain (2)

Pediatric Psoriasis Hospitalization Cases (5)

The five hospitalization cases in psoriasis patients are a subset of the 200 hospitalizations identified in section 3.1.1. Of these five cases (US 4, foreign 1), two cases were associated with gastro-intestinal illnesses, one of which was a ruptured appendix; one case was associated with bilateral pneumonia that occurred during etanercept treatment; and one case reported a “severe anaphylaxis” reaction within 24 hours of the etanercept dose. The final hospitalization event did not appear to be related to etanercept, since etanercept had been discontinued at least six months prior to the onset of the patient’s hospitalization. One of five cases described the extent of the patient’s psoriasis (widespread, more than 20% coverage); and two of five cases reported prior psoriasis treatment including methotrexate, cyclosporine, and/or topical corticosteroids.

A brief description of the hospitalization cases follow:

AERS ISR# 5627996, US, Hospitalization, 2008

This 15 year old male received Enbrel at an unreported frequency and dose to treat psoriasis for 4 years. After 4 years of treatment the patient developed flu-like symptoms and Enbrel was discontinued. The week following discontinuation the patient developed bilateral pneumonia and was subsequently hospitalized in the intensive care unit and treatment included unspecified antibiotics. No further details were provided. The case did not provide information concerning past treatments for the patient’s psoriasis.

AERS ISR# 5470921, US, Hospitalization, 2007

This 11 year old female received Enbrel 50mg twice weekly for psoriasis and was hospitalized for a ruptured appendix and associated symptoms. The patient had received Enbrel for one year and 3 months. During hospitalization the patient had a second surgery for a “pocket of infection” in the abdomen. The patient was in the critical care unit, and the event was described as ongoing.

AERS ISR# 5321094, Foreign, Hospitalization, 2007

This 17 year old female with psoriasis received Enbrel 25mg twice weekly was hospitalized for “gastric complaints” five months after initiation of therapy. Enbrel was discontinued upon hospitalization. The patient was diagnosed with “hypereosinophilia.”

AERS ISR# 4919025, US, Hospitalization, 2004

This 17 year old female was hospitalized with erythrodermic psoriasis and fever that occurred during treatment with efalizumab. Etanercept 50mg twice weekly had been discontinued six months prior to the onset of the erythrodermic psoriasis. Adverse events potentially associated with etanercept use included optic neuritis, blurred vision and persistent numbness in her left arm and thigh. These events did not result in hospitalization. This patient also concomitantly used cyclosporine, and had previously used efalizumab, methotrexate and corticosteroids.

AERS ISR# 4117720, US, Hospitalization, 2003

This 16 year old female was diagnosed with "severe anaphylaxis" and hospitalized one day after receiving her first dose of Enbrel (25mg twice weekly) to treat psoriasis. The patient experienced low blood pressure, nausea and vomiting and an extensive erythematous rash. The patient was not taking concomitant medications, and did not have any document allergies. No further information was provided, and the reporter did not indicate if the patient continued to receive etanercept after the episode.

3.9 DRUG UTILIZATION DATA RESULTS

3.9.1 Etanercept Prescription Dispensing and Patient Demographics

The projected number of prescriptions dispensed for etanercept rose from 444,614 during 2002 to 823,698 during 2005 before falling to 774,910 during 2007, a 74% increase in volume (Appendix 1, Table 1). Patients age 0-3 years old accounted for 0.1% or less of the yearly prescriptions dispensed, patients age 4-17 years old accounted for 2-3% of yearly prescription volume and adults accounted for 97-98% of yearly prescription volume.

The number of prescriptions dispensed to 4-17 year old patients rose from 9,774 during 2002 to 19,905 during 2007, a 104% increase. Among these patients we examined subgroups of ages 4-11 years old and 12-17 years old. The number of prescriptions dispensed to the 4-11 year olds rose from 3,982 (41% of the 4-17 year old dispensing) during 2002 to 7,043 prescriptions during 2007 (35% of the 4-17 year old dispensing), a relative increase of 77%. Prescriptions dispensed to the 12-17 year old subgroup rose from 5,762 during 2002 (59% of the 4-17 year old dispensing) to 12,862 during 2007 (65% of the 4-17 year old dispensing), a relative increase of 123%.

3.9.2 Etanercept Prescribing Physician Specialty

We examined the top 10 prescribing physician specialties (based on 2007 prescription volume) for the years 2002 through 2007 using Verispan's Vector One: National (Appendix 2, Table 2). The most common prescribing specialty for etanercept during each year was the rheumatology specialty which accounted for 71% of prescriptions during 2002 and 59% of prescriptions during 2007. Prescriptions associated with dermatologists rose dramatically from 3,000 during 2002 to 104,000 during 2007, the largest increase among the examined physician specialties.

3.9.3 Retail Patient Counts

We obtained projected estimates of the number of patients who received a prescription for etanercept through outpatient retail pharmacies using Verispan's Total Patient Tracker for the years 2002 through 2007. The projected number of patients who received a prescription for etanercept rose from 71,489 during 2002 to 143,818 during 2005 then declined slightly to 141,233 patients during 2007 (Appendix 2, Table 3). Overall, there was an increase in patient volume of 98% over the 6 year study period.

Patients in the 4-17 year old subgroup accounted for approximately 3% of the etanercept patient volume during each year examined. The number of patients in this group rose from 1,955 during 2002 to 4,301 during 2007, a 120% relative increase. Among this subgroup, 35-42% were aged 4-11 years old and 62-67% were 12-17 years old. The 12-17 year old subgroup experienced the largest relative increase in this study rising from 1,212 during 2002 to 2,881 during 2007, a 138% increase.

3.9.4 Physician Prescribing Practices

We obtained data for the most common diagnoses associated with a mention of etanercept for a pediatric patient by office based physicians using Verispan's Physician Drug and Diagnosis Audit. Use within the pediatric population was too low to examine yearly trends due to the small sample size resulting in instability in the projected estimates. We therefore aggregated the data into a cumulative total for the years 2002 through 2007 (Table 11, below). The total number of etanercept physician mentions for all patients during this time period was 4 million. Pediatric patients 0-17 years of age accounted for 75,000 (1.9%) of those mentions. The most commonly mentioned diagnosis among pediatric patients was "juvenile chronic polyarthritis (ICD-9 714.3) which accounted for 36% of etanercept associated mentions, followed by "other psoriasis (ICD-9 696.1) with 15% of mentions.

Table 11. Diagnoses associated for a mention of etanercept in pediatric patients (in thousands)

	January 2002-December 2007	
	Thousands of Uses (%)	
Etanercept	4,012	(100)
0-17 years old	75	(1.9)
7143 Juv Chron Polyarthritis	27	(36)
6961 Other Psoriasis	11	(14.7)
7165 Polyarthritis Nos	6	(8)
7291 Myalgia And Myositis Nos	6	(8)
7209 Inflamm Spondylopathy Nos	5	(6.7)
7219 Spondylosis Nos	5	(6.7)
7101 Systemic Sclerosis	4	(5.3)
7200 Ankylosing Spondylitis	4	(5.3)
7040 Alopecia	3	(4)
7140 Rheumatoid Arthritis	2	(2.7)
18+	3,753	(93.5)
UNSPEC.	184	(4.6)

Source: Verispan Physician Drug and Diagnosis Audit, Extracted 4/2008,
File: 2008-339 Enbrel diagnoses by age.qry

4 DISCUSSION

4.1 ADVERSE EVENTS

DAEA reviewed all post-marketing pediatric cases retrieved from the Adverse Event Reporting System (AERS) with an outcome of death; and the majority (8 of 14 cases) occurred in patients who received etanercept for Juvenile Idiopathic Arthritis (JIA), which is the only approved

indication for pediatric patients at this time. The most commonly reported cause of death was due to infectious complications. In addition, our review of serious domestic safety events in pediatric patients also showed that infections were the most commonly reported events that resulted in other serious outcomes, including hospitalization and/or life-threatening outcomes (n=31). Although etanercept labeling contains a bolded warning about the risk of serious infections, including sepsis and fatalities resulting from infections, the occurrence of sepsis resulting in death and other serious outcomes in pediatric population was concerning. The time to onset in our case series showed that infection may occur as late as four years after initiation of etanercept, and indicated that continued vigilance is required to monitor for infection-related complication while a pediatric patient is receiving etanercept.

Our review of domestic pediatric cases with serious outcomes showed that aside from infections, other commonly reported serious events were neurologic (n=10), gastrointestinal/hepatobiliary (n=9), musculoskeletal (n=8), and hematologic (n=6) events. Serious hematologic events of concern such as aplastic anemia and pancytopenia were reported; these events are labeled under Warnings section. There were 12 miscellaneous reports, which included other significant adverse events such as diabetes mellitus (n=3), systemic lupus erythematosus (n=2), and hypersensitivity reactions (n=2). One case of diabetes reported recurrence of diabetic ketoacidosis with reintroduction of etanercept therapy. Overall, most of these were qualitatively similar to adverse events already reflected in the etanercept labeling.

Nine **malignancies** (US 5, Foreign 4) were reported in pediatric patients who received etanercept. Three of nine were lymphoma cases in JIA patients. Although lymphoma has been associated in adults who received anti-TNF therapy (including etanercept), lymphoma is not a known complication of JIA, and the occurrence of these pediatric cases along with cases reported with other anti-TNF agents have been brought to the Agency's attention. Currently, the Agency is evaluating the significance of these, as well as cases of lymphoma and malignancies reported with other anti-TNF agents, and OSE is conducting a comprehensive review of all post-marketing malignancy cases associated with all anti-TNF agents. However, because of long latency, there may be a significant time lag between the use of product and development and reporting of malignancies. Also, current etanercept usage estimate in children appear to be fairly small (section 3.9); thus, the risk of malignancies in pediatric population may potentially increase over time if overall exposure (including duration of exposure) in children increases in the future.

Macrophage activation syndrome (MAS) is a known complication of JIA, and triggers of MAS include viral infections (such as EBV), non-steroidal anti-inflammatory drugs (NSAIDs), sulfasalazine, and methotrexate (MTX) therapy.¹ All thirteen MAS cases reported with etanercept occurred in patients with JIA; and nine of thirteen MAS cases were confounded by either JIA flare or EBV/viral infection. In addition, nine of thirteen cases were confounded by concomitant medications such as MTX, NSAIDs, and sulfasalazine. However, the concomitant medications appeared to have been chronic medications and the reported MAS events were temporally associated with etanercept therapy in all cases. In addition, as anti-TNF agents have been known to reactivate EBV², it is biologically plausible that etanercept may cause reactivation of EBV and precipitate MAS in some susceptible patients.

We reviewed ten cases of **varicella** reported with etanercept therapy, six of which resulted in hospitalizations due to varicella. Two of ten cases reported previous history of varicella, and thus appear to be reactivated diseases. One of ten cases was diagnosed with primary varicella infection, and another case reported exposure at the patient's school. The remaining six cases did not provide diagnosis or exposure information. Five of ten cases reported improvement; the remaining five cases did not provide outcome information. The labeling of etanercept discusses

the occurrence of varicella infections in JIA patients and recommends that all immunizations be updated in JIA patients before initiating etanercept.

There were two foreign cases of **tuberculosis** reported in pediatric patients who received etanercept therapy in AERS. A comprehensive OSE review of tuberculosis associated with etanercept has been conducted previously¹⁵, and the labeling of etanercept has been updated based on the recommendations from that review. In adults, cases of tuberculosis associated with anti-TNF agents have resulted in atypical manifestations such as disseminated, non-pulmonary disease, with some cases resulting in fatal outcome.

Based on our current review and previous review of post-marketing events in children³, adverse events observed in pediatric population were qualitatively similar to those observed in adult population; also, similar to adults, some of these events lead to serious outcomes including deaths and hospitalizations. The risks associated with etanercept therapy in adult population are better known and multiple events have been evaluated, across multiple indications. Given the small exposure in pediatric population and small post-marketing safety data, especially in children with psoriasis, there is no evidence that the risk in children is different from those observed in adults, where significant safety concerns exist. This should be considered as we assess the overall benefit/risk for the proposed pediatric psoriasis indication for etanercept.

4.2 DRUG UTILIZATION DATA

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that etanercept was distributed primarily to the outpatient mail order and retail pharmacy settings based on the IMS Health, IMS National Sales PerspectivesTM. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these pharmacies may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use. The mail order channel represents a substantial proportion of the purchases of these products (over 50% during 2007) and is a significant limitation in this analysis.

Indications for use were obtained using Verispan's PDDA, a survey of 3,200 office based physicians. Although PDDA data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. Mentions of etanercept for the pediatric population were rare (1 to 7 unprojected physician mentions per year in the Verispan sample). In general, PDDA data are best used to identify the typical uses for the products in clinical practice, and the VONA outpatient prescription data to evaluate trends over time.

5 RECOMMENDATIONS AND CONCLUSION

Our post-marketing review demonstrated that etanercept therapy was associated with serious adverse events in pediatric population such as infections and malignancies, similar to adults. Given that the drug usage in pediatric population is estimated to be fairly small at this time, the numbers and types of post-marketing adverse events reported are concerning. Many of these events, especially infection-related complications such as sepsis, were life-threatening and resulted in deaths and hospitalizations. Long-term potential toxicities such as malignancies and neurologic events are especially worrisome in children with plaque psoriasis who will likely receive etanercept therapy chronically. Thus, given these considerable risks associated with

etanercept, the benefit of this therapy in children with plaque psoriasis would need to be substantial in order to justify its approval and usage in the pediatric plaque psoriasis population.

Following labeling changes are recommended regardless of pediatric psoriasis application outcome:

- The current etanercept labeling describes adverse events observed in the pediatric population under the '*Adverse Reactions in Patients with JIA*', and the labeling states that "the types of infections reported in JIA patients were generally mild and consistent with those commonly seen in outpatient pediatric populations". DAEA recommends enhancing the labeling to reflect that etanercept therapy in pediatric patients may lead to moderate to severe infections and can result in serious outcomes, including deaths and hospitalizations.
- DAEA recommends updating the serious adverse events reported in pediatric patients in post-marketing experience under the '*Adverse Reactions in Patients with JIA*' section with the following adverse events: macrophage activation syndrome, malignancies, diabetes mellitus, and systemic lupus erythematosus.
- A medication guide as previously recommended by OSE on March 27, 2007 review.

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APPENDICES

APPENDIX 1- DRUG UTILIZATION DATA TABLES

Table 1. Projected Number of Retail Prescriptions Dispensed for Etanercept, By Patient Age for the Years 2002 - 2007

	2002		2003		2004		2005		2006		2007	
	Retail TRxs	(%)										
etanercept	444,614	(100)	665,525	(100)	772,710	(100)	823,698	(100)	786,287	(100)	774,910	(100)
0-3	124	(0)	355	(0.1)	434	(0.1)	301	(0)	433	(0.1)	331	(0)
4-17	9,744	(2.2)	14,711	(2.2)	17,643	(2.3)	18,363	(2.2)	18,640	(2.4)	19,905	(2.6)
4-11	3,982	(0.9)	5,299	(0.8)	5,871	(0.8)	6,652	(0.8)	6,511	(0.8)	7,043	(0.9)
12-17	5,762	(1.3)	9,412	(1.4)	11,772	(1.5)	11,711	(1.4)	12,129	(1.5)	12,862	(1.7)
18+	433,954	(97.6)	649,047	(97.5)	750,864	(97.2)	799,809	(97.1)	764,727	(97.3)	752,874	(97.2)
Unspec.	792	(0.2)	1,412	(0.2)	3,769	(0.5)	5,225	(0.6)	2,487	(0.3)	1,800	(0.2)

Source: Verispan Vector One: National, Data Extracted 8/2008, File:2008-339 VONA Etanercept age

Table 2. Projected Number of Retail Prescriptions Dispensed for Etanercept, By Prescribing Physician Specialty, Years 2002 – 2007 (in thousands)

	2002		2003		2004		2005		2006		2007	
	Retail TRxs	(%)										
	(000)		(000)		(000)		(000)		(000)		(000)	
Total	445	(100)	666	(100)	773	(100)	824	(100)	786	(100)	775	(100)
Rheumatology	314	(70.6)	430	(64.6)	452	(58.5)	464	(56.3)	463	(58.9)	455	(58.8)
Dermatology	3	(0.7)	55	(8.3)	98	(12.7)	120	(14.5)	105	(13.4)	104	(13.4)
Internal Med	47	(10.6)	65	(9.8)	72	(9.3)	75	(9.1)	74	(9.4)	71	(9.2)
Unspecified	40	(9)	53	(7.9)	75	(9.7)	75	(9.1)	48	(6.1)	45	(5.8)
GP/FM/DO*	12	(2.8)	17	(2.5)	20	(2.6)	25	(3)	28	(3.6)	30	(3.9)
Hospitalist	5	(1.1)	10	(1.5)	13	(1.7)	16	(2)	16	(2)	15	(1.9)
Pediatrician	6	(1.3)	8	(1.2)	9	(1.2)	10	(1.2)	11	(1.3)	12	(1.5)
Phys. Assist	1	(0.3)	3	(0.5)	6	(0.8)	8	(0.9)	9	(1.1)	11	(1.5)
Nurse Pract.	1	(0.3)	3	(0.5)	5	(0.7)	7	(0.9)	9	(1.2)	10	(1.3)
Aller/Immu	4	(0.9)	5	(0.7)	5	(0.6)	6	(0.7)	5	(0.7)	5	(0.7)
Others	11	(2.4)	16	(2.3)	17	(2.1)	19	(2.3)	18	(2.3)	17	(2.2)

Source: Verispan Vector One: National, Data Extracted 8/2008, File:2008-339 VONA Etanercept MD

* General Practitioners, Family Medicine physicians, and Doctors of Osteopathy

Table 3. Projected Number of Patients who Received an Etanercept Prescription Through U.S. Outpatient Retail Pharmacies, By Age, Years 2002-2007

	2002		2003		2004		2005		2006		2007	
	Patients*	(%)	Patients	(%)								
Grand Total	71,489	(100)	129,107	(100)	135,900	(100)	143,818	(100)	142,791	(100)	141,233	(100)
0 - 3	48	(0.1)	159	(0.1)	157	(0.1)	104	(0.1)	133	(0.1)	96	(0.1)
4 - 17	1,955	(2.7)	3,399	(2.6)	3,838	(2.8)	3,866	(2.7)	3,975	(2.8)	4,301	(3)
4 - 11	816	(41.7)	1,351	(39.7)	1,382	(36)	1,496	(38.7)	1,427	(35.9)	1,521	(35.4)
12 - 17	1,212	(62)	2,173	(63.9)	2,582	(67.3)	2,485	(64.3)	2,672	(67.2)	2,881	(67)
18+	69,607	(97.4)	125,473	(97.2)	131,438	(96.7)	139,164	(96.8)	138,405	(96.9)	136,753	(96.8)
Unknown	110	(0.2)	715	(0.6)	1,671	(1.2)	2,155	(1.5)	1,259	(0.9)	1,025	(0.7)

Source: Verispan Total Patient Tracker, Extracted 4/2008, Source File: 2008-339 TPT Etanercept age.xls

*columns will not sum correctly due to patient aging during the study period.

APPENDIX 2- DRUG UTILIZATION DATABASE DESCRIPTIONS

Verispan, LLC: Vector One®: National (VONA)

Verispan's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One receives over 2 billion prescription claims, representing over 160 million unique patients.

Prescriptions are captured from a sample of approximately 54,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent approximately 50% of retail prescriptions dispensed nationwide. Verispan receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

Verispan, LLC: Vector One®: Total Patient Tracker (TPT)

Verispan's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector one receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

Verispan, LLC: Physician Drug & Diagnosis Audit® (PDDA)

Verispan's Physician Drug & Diagnosis Audit (PDDA) is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from approximately 3,100 office-based physicians representing 29 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Verispan uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

IMS Health, IMS National Sales Perspectives™, Retail and Non-Retail

The IMS Health, IMS National Sales Perspective™ measures the volume of drug products (both prescription and over-the-counter) and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass Merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products moving from manufacturer into retail and non-retail settings in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections.

Appendix 3 – Adverse Event Reporting System (AERS) Description and Limitations

AERS is a collection of spontaneously submitted adverse event reports, with the earliest report dating back to 1969. The reports are submitted from a variety of sources (domestic, foreign, literature). Reports come to the FDA either directly from health professionals or consumers, or from pharmaceutical manufacturers.

Limitations:

- The recognition of an adverse event associated with a drug product is subjective and imprecise. Failure to recognize the association between a drug and event may be further complicated in cases where there is a latency period between exposure to the drug product and occurrence of the observed event.
- Under-reporting is a limitation of spontaneous reporting systems. It has been estimated that the FDA receives approximately 1 to 10% of suspected serious adverse event reports.
- Report quality varies.
- Reporting is subject to biases. Unlike clinical trial data, which are obtained under strictly controlled conditions, spontaneously submitted report information is uncontrolled and subjected to a number of biases, including the length of time a product has been on the market. In addition to these biases, it is possible that reported cases might differ from non-reported cases in characteristics such as time to onset or severity.
- Spontaneous reporting systems lack denominator data, such as user population and drug exposure patterns, and therefore cannot be used to derive incidence data.

Strengths:

- Spontaneous reporting systems maintain ongoing surveillance of all patients, and are relatively inexpensive. Spontaneous reporting systems are the most common method used in pharmacovigilance to generate signals on new or rare adverse events not discovered during clinical trials.
- The great utility of spontaneous reports lies in hypothesis generation. By raising suspicions, spontaneous reporting systems generate signals of potential problems that warrant further investigation.

Appendix 4: The 20 most commonly reported post-marketed adverse events in all patients treated with etanercept from marketing to April 22, 2008

The number of reports is a crude number; duplicate reports have not been reconciled; a report may contain more than one adverse event term, and causality has not been assessed.

Etanercept Post Marketing Crude Reports from marketing to April 22, 2008, All Ages, Locations

Etanercept (n = 54,710)	# of Reports	Label Status
Injection Site Reaction	6195	Labeled
Injection Site Pain	3993	Labeled
Rheumatoid Arthritis	2444	Indication
Injection Site Haemorrhage	2354	Labeled
Headache	2227	Labeled
Condition Aggravated	1949	*
Injection Site Bruising	1794	Labeled
Drug Ineffective	1799	Not Applicable
Sinusitis	1709	Labeled
Arthralgia	1699	Labeled as joint pain
Injection site erythema	1645	Labeled
Injection site irritation	1507	Labeled
Nausea	1464	Labeled
Pain	1455	Labeled
Psoriasis	1452	Potential indication
Cough	1439	Labeled
Pyrexia	1437	Labeled
Upper Respiratory Tract Infection	1403	Labeled
Dermatitis	1367	Labeled as rash
Asthenia	1291	Labeled

* Labeled for worsening psoriasis and worsening lung disorder

Appendix 5: The 20 most commonly reported post-marketed adverse events in pediatric patients aged 4 to 17 years old treated with adalimumab and infliximab from Marketing to April 8, 2008

The number of reports is a crude number; duplicate reports have not been reconciled; a report may contain more than one adverse event term; and causality has not been assessed.

Adalimumab (n = 148)		Infliximab (n = 792)	
Adverse Event Term	# of Reports	Adverse Event Term	# of Reports
Injection Site Irritation	32	Infusion Related Reaction	89
Injection Site Pain	29	Dyspnoea	88
Accidental Exposure	21	Pyrexia	70
Drug Ineffective	12	Crohn's Disease	55
Crohn's Disease	7	Vomiting	42
Headache	6	Flushing	41
Injection Site Erythema	6	Abdominal Pain	39
Fatigue	5	Rash	34
Pain	5	Headache	33
Pyrexia	5	Chest Pain	32
Injection Site Haemorrhage	4	Arthralgia	30
Injection Site Reaction	4	Nausea	28
Injection Site Swelling	4	Anaphylactic Reaction	26
Muscle Spasms	4	Condition Aggravated	25
Psoriasis	4	Chest Discomfort	22
Rash	4	Colitis Ulcerative	22
Anorexia	3	Erythema	22
Arthralgia	3	Urticaria	21
Injection Site Bruising	3	Drug Ineffective	20
Injection Site Rash	3	Hypersensitivity	20

ENBREL[®] (etanercept)

For Subcutaneous Injection

WARNING **RISK OF INFECTIONS**

Infections, including serious infections leading to hospitalization or death, have been observed in patients treated with ENBREL[®] (see **WARNINGS** and **ADVERSE REACTIONS**). Infections have included bacterial sepsis and tuberculosis. Patients should be educated about the symptoms of infection and closely monitored for signs and symptoms of infection during and after treatment with ENBREL[®]. Patients who develop an infection should be evaluated for appropriate antimicrobial treatment and, in patients who develop a serious infection, ENBREL[®] should be discontinued.

Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation) has been observed in patients receiving TNF-blocking agents, including ENBREL[®]. Tuberculosis may be due to reactivation of latent tuberculosis infection or to new infection. Data from clinical trials and preclinical studies suggest that the risk of reactivation of latent tuberculosis infection is lower with ENBREL[®] than with TNF-blocking monoclonal antibodies. Nonetheless, postmarketing cases of tuberculosis reactivation have been reported for TNF blockers, including ENBREL[®]. Patients should be evaluated for tuberculosis risk factors and be tested for latent tuberculosis infection prior to initiating ENBREL[®] and during treatment. Treatment of latent tuberculosis 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.

DESCRIPTION

ENBREL[®] (etanercept) is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) tumor necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1. The Fc component of etanercept contains the C_H2 domain, the C_H3 domain and hinge region, but not the C_H1 domain of IgG1. Etanercept is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system. It consists of 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons.

ENBREL[®] single-use prefilled syringes are available in 25 mg (0.51 mL of a 50 mg/mL solution of etanercept) and 50 mg (0.98 mL of a 50 mg/mL solution of etanercept) dosage

strengths. **ENBREL[®] single-use prefilled SureClick[™] autoinjectors** are available in 50 mg (0.98 mL of a 50 mg/mL solution of etanercept).

The solution of ENBREL[®] is clear and colorless, sterile, preservative-free, and is formulated at pH 6.3 ± 0.2 . Each ENBREL[®] prefilled syringe and SureClick[™] autoinjector contains a 50 mg/mL solution of etanercept with 1% sucrose, 100 mM sodium chloride, 25mM L-arginine hydrochloride, and 25mM sodium phosphate.

ENBREL[®] multiple-use vials are available containing 25 mg of etanercept. ENBREL[®] is supplied in a multiple-use vial as a sterile, white, preservative-free, lyophilized powder. Reconstitution with 1 mL of the supplied Sterile Bacteriostatic Water for Injection (BWFI), USP (containing 0.9% benzyl alcohol) yields a multiple-use, clear, and colorless solution with a pH of 7.4 ± 0.3 containing 25 mg etanercept, 40 mg mannitol, 10 mg sucrose, and 1.2 mg tromethamine.

Administration of one 50 mg ENBREL[®] prefilled syringe or one ENBREL[®] SureClick[™] autoinjector provides a dose equivalent to two 25 mg ENBREL[®] prefilled syringes or two multiple-use vials of lyophilized ENBREL[®], when vials are reconstituted and administered as recommended.

CLINICAL PHARMACOLOGY

General

Etanercept binds specifically to tumor necrosis factor (TNF) and blocks its interaction with cell surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. It plays an important role in the inflammatory processes of rheumatoid arthritis (RA), polyarticular-course juvenile idiopathic arthritis (JIA), and ankylosing spondylitis and the resulting joint pathology. In addition, TNF plays a role in the inflammatory process of plaque psoriasis. Elevated levels of TNF are found in involved tissues and fluids of patients with RA, psoriatic arthritis, ankylosing spondylitis (AS), and plaque psoriasis.

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 α and TNF β (lymphotoxin alpha [LT α]) 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.

Etanercept can also modulate biological responses that are induced or regulated by TNF, including expression of adhesion molecules responsible for leukocyte migration (i.e., E-selectin and to a lesser extent intercellular adhesion molecule-1 [ICAM-1]), serum levels of cytokines (e.g., IL-6), and serum levels of matrix metalloproteinase-3 (MMP-3 or stromelysin).

Pharmacokinetics

After administration of 25 mg of ENBREL[®] by a single subcutaneous (SC) injection to 25 patients with RA, a mean \pm standard deviation half-life of 102 ± 30 hours was observed with a clearance of 160 ± 80 mL/hr. A maximum serum concentration (C_{max}) of 1.1 ± 0.6 mcg/mL and time to C_{max} of 69 ± 34 hours was observed in these patients following a single 25 mg dose. After 6 months of twice weekly 25 mg doses in these same RA patients, the mean C_{max} was 2.4 ± 1.0 mcg/mL (N = 23). Patients exhibited a two- to seven-fold increase in peak serum concentrations and approximately four-fold increase in AUC_{0-72 hr} (range 1 to 17 fold) with repeated dosing. Serum concentrations in patients with RA have not been measured for periods of dosing that exceed 6 months. The pharmacokinetic parameters in patients with plaque psoriasis were similar to those seen in patients with RA.

In another study, serum concentration profiles at steady state were comparable among patients with RA treated with 50 mg ENBREL[®] once weekly and those treated with 25 mg ENBREL[®] twice weekly. The mean (\pm standard deviation) C_{max}, C_{min}, and partial AUC were 2.4 ± 1.5 mg/L, 1.2 ± 0.7 mg/L, and 297 ± 166 mg•h/L, respectively, for patients treated with 50 mg ENBREL[®] once weekly (N = 21); and 2.6 ± 1.2 mg/L, 1.4 ± 0.7 mg/L, and 316 ± 135 mg•h/L for patients treated with 25 mg ENBREL[®] twice weekly (N = 16).

Pharmacokinetic parameters were not different between men and women and did not vary with age in adult patients. No formal pharmacokinetic studies have been conducted to examine the effects of renal or hepatic impairment on ENBREL[®] disposition.

Patients with JIA (ages 4 to 17 years) were administered 0.4 mg/kg of ENBREL[®] twice weekly for up to 18 weeks. The mean serum concentration after repeated SC dosing was 2.1 mcg/mL, with a range of 0.7 to 4.3 mcg/mL. Limited data suggests that the clearance of ENBREL[®] is reduced slightly in children ages 4 to 8 years. Population pharmacokinetic analyses predict that administration of 0.8 mg/kg of ENBREL[®] once weekly will result in C_{max} 11% higher, and C_{min} 20% lower at steady state as compared to administration of 0.4 mg/kg of ENBREL[®] twice weekly. The predicted pharmacokinetic differences between the regimens in JIA patients are of the same magnitude as the differences observed between twice weekly and weekly regimens in adult RA patients.

CLINICAL STUDIES

Adult Rheumatoid Arthritis

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

Study I evaluated 234 patients with active RA who were ≥ 18 years old, had failed therapy with at least one but no more than four disease-modifying antirheumatic drugs (DMARDs; e.g., hydroxychloroquine, oral or injectable gold, methotrexate [MTX], azathioprine, D-penicillamine, sulfasalazine), and had ≥ 12 tender joints, ≥ 10 swollen joints, and either ESR ≥ 28 mm/hr, CRP > 2.0 mg/dL, or morning stiffness for ≥ 45 minutes. Doses of 10 mg or 25 mg ENBREL[®] or

placebo were administered SC twice a week for 6 consecutive months. Results from patients receiving 25 mg are presented in Table 1.

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

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

Study IV evaluated 682 adult patients with active RA of 6 months to 20 years duration (mean of 7 years) who had an inadequate response to at least one DMARD other than MTX. Forty-three percent of patients had previously received MTX a mean of two years prior to the trial at a mean dose of 12.9 mg. Patients were excluded from this study if MTX had been discontinued for lack of efficacy or for safety considerations. The patient baseline characteristics were similar to those of patients in Study I (Table 3). Patients were randomized to MTX alone (7.5 to 20 mg weekly, dose escalated as described for Study III; median dose 20 mg), ENBREL[®] alone (25 mg twice weekly), or the combination of ENBREL[®] and MTX initiated concurrently (at the same doses as above). The study evaluated ACR response, Sharp radiographic score and safety.

Clinical Response

A higher percentage of patients treated with ENBREL[®] and ENBREL[®] in combination with MTX achieved ACR 20, ACR 50, and ACR 70 responses and Major Clinical Responses than in the comparison groups. The results of Studies I, II, and III are summarized in Table 1. The results of Study IV are summarized in Table 2.

Table 1:
ACR Responses in Placebo- and Active-Controlled Trials
(Percent of Patients)

Response	Placebo Controlled				Active Controlled	
	Study I		Study II		Study III	
	Placebo	ENBREL ^{®a}	MTX/ Placebo	MTX/ ENBREL ^{®a}	MTX	ENBREL ^{®a}
	N = 80	N = 78	N = 30	N = 59	N = 217	N = 207
<u>ACR 20</u>						
Month 3	23%	62% ^b	33%	66% ^b	56%	62%
Month 6	11%	59% ^b	27%	71% ^b	58%	65%
Month 12	NA	NA	NA	NA	65%	72%
<u>ACR 50</u>						
Month 3	8%	41% ^b	0%	42% ^b	24%	29%
Month 6	5%	40% ^b	3%	39% ^b	32%	40%
Month 12	NA	NA	NA	NA	43%	49%
<u>ACR 70</u>						
Month 3	4%	15% ^b	0%	15% ^b	7%	13% ^c
Month 6	1%	15% ^b	0%	15% ^b	14%	21% ^c
Month 12	NA	NA	NA	NA	22%	25%

^a 25 mg ENBREL[®] SC twice weekly.

^b p < 0.01, ENBREL[®] vs. placebo.

^c p < 0.05, ENBREL[®] vs. MTX.

Table 2:
Study IV Clinical Efficacy Results: Comparison of MTX vs ENBREL® vs ENBREL®
in Combination with MTX in Patients with RA
of 6 Months to 20 Years Duration
(Percent of Patients)

Endpoint	MTX (N = 228)	ENBREL® (N = 223)	ENBREL®/MTX (N = 231)
<u>ACR N^{a, b}</u>			
Month 12	40	47	63 ^c
<u>ACR 20</u>			
Month 12	59%	66%	75% ^c
<u>ACR 50</u>			
Month 12	36%	43%	63% ^c
<u>ACR 70</u>			
Month 12	17%	22%	40% ^c
Major Clinical Response^d	6%	10%	24% ^c

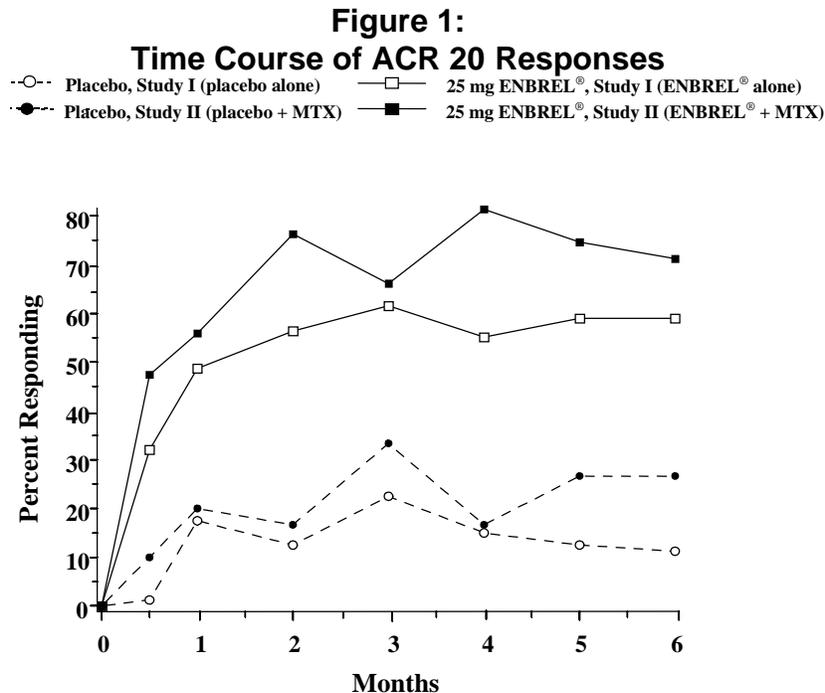
^a Values are medians.

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

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

^d Major clinical response is achieving an ACR 70 response for a continuous 6-month period.

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



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 in Studies I and III: 25 mg ENBREL[®] was more effective than 10 mg (10 mg was not evaluated in Study II). ENBREL[®] was significantly better than placebo in all components of the ACR criteria as well as other measures of RA disease activity not included in the ACR response criteria, such as morning stiffness.

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

The results of the components of the ACR response criteria for Study I are shown in Table 3. Similar results were observed for ENBREL[®]-treated patients in Studies II and III.

Table 3:
Components of ACR Response in Study I

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

* Results at 6 months showed similar improvement.

^a 25 mg ENBREL[®] SC twice weekly.

^b Scale 0 – 71.

^c Scale 0 – 68.

^d Visual analog scale; 0 = best, 10 = worst.

^e Health Assessment Questionnaire¹; 0 = best, 3 = worst; includes eight categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

^f $p < 0.01$, ENBREL[®] vs. placebo, based on mean percent change from baseline.

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

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

A 24-week study was conducted in 242 patients with active RA on background methotrexate who were randomized to receive either ENBREL[®] alone or the combination of ENBREL[®] and anakinra. The ACR 50 response rate was 31% for patients treated with the combination of ENBREL[®] and anakinra and 41% for patients treated with ENBREL[®] alone, indicating no added clinical benefit of the combination over ENBREL[®] alone. Serious infections were increased with the combination compared to ENBREL[®] alone (see **WARNINGS**).

Physical Function Response

In Studies I, II, and III, physical function and disability were assessed using the Health Assessment Questionnaire (HAQ).¹ Additionally, in Study III, patients were administered the SF-36² Health Survey. In Studies I and II, patients treated with 25 mg ENBREL[®] twice weekly showed greater improvement from baseline in the HAQ score beginning in month 1 through month 6 in comparison to placebo ($p < 0.001$) for the HAQ disability domain (where 0 = none

and 3 = severe). In Study I, the mean improvement in the HAQ score from baseline to month 6 was 0.6 (from 1.6 to 1.0) for the 25 mg ENBREL[®] group and 0 (from 1.7 to 1.7) for the placebo group. In Study II, the mean improvement from baseline to month 6 was 0.6 (from 1.5 to 0.9) for the ENBREL[®]/MTX group and 0.2 (from 1.3 to 1.2) for the placebo/MTX group. In Study III, the mean improvement in the HAQ score from baseline to month 6 was 0.7 (from 1.5 to 0.7) for 25 mg ENBREL[®] twice weekly. All subdomains of the HAQ in Studies I and III were improved in patients treated with ENBREL[®]. In Study III, patients treated with 25 mg ENBREL[®] twice weekly showed greater improvement from baseline in SF-36 physical component summary score compared to ENBREL[®] 10 mg twice weekly and no worsening in the SF-36 mental component summary score. In open-label ENBREL[®] studies, improvements in physical function and disability measures have been maintained for up to 4 years.

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

Radiographic Response

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

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

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

* 95% confidence intervals for the differences in change scores between MTX and ENBREL[®].

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

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

In Study IV, less radiographic progression (TSS) was observed with ENBREL[®] in combination with MTX compared with ENBREL[®] alone or MTX alone at month 12 (Table 5). In the MTX treatment group 55% of patients experienced no radiographic progression (TSS change \leq 0.0) at 12 months compared to 63% and 76% in the ENBREL[®] alone and the ENBREL[®]/MTX combination treatment groups, respectively.

**Table 5:
Mean Radiographic Change in Study IV at 12 Months
(95% Confidence Interval)**

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

* Analyzed radiographic ITT population.

^a p < 0.05 for comparison of ENBREL[®] vs MTX.

^b p < 0.05 for comparison of ENBREL[®]/MTX vs MTX.

^c p < 0.05 for comparison of ENBREL[®]/MTX vs ENBREL[®].

Once Weekly Dosing

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

Polyarticular-Course Juvenile Idiopathic Arthritis (JIA)

The safety and efficacy of ENBREL[®] were assessed in a two-part study in 69 children with polyarticular-course JIA who had a variety of JIA onset types. Patients ages 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 nonsteroidal 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 randomized 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),³ defined as $\geq 30\%$ improvement in at least three of six and $\geq 30\%$ worsening in no more than one of the six JIA core set criteria, including active joint count, limitation of motion, physician and patient/parent global assessments, functional assessment, and ESR. Disease flare was defined as a $\geq 30\%$ worsening in three of the six JIA core set criteria and $\geq 30\%$ improvement in not more than one of the six JIA core set criteria and a minimum of two active joints.

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

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

Studies have not been done in patients with polyarticular-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.

Psoriatic Arthritis

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

Compared to placebo, treatment with ENBREL[®] resulted in significant improvements in measures of disease activity (Table 6).

Table 6:
Components of Disease Activity in Psoriatic Arthritis

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

^a $p < 0.001$ for all comparisons between ENBREL[®] and placebo at 6 months.

^b Scale 0 – 78.

^c Scale 0 – 76.

^d Likert scale; 0 = best, 5 = worst.

^e Health Assessment Questionnaire¹; 0 = best, 3 = worst; includes eight categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

^f Normal range: 0 – 0.79 mg/dL.

Among patients with 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. Responses were similar in patients who were or were not receiving concomitant methotrexate therapy at baseline. At 6 months, the ACR 20/50/70 responses were achieved by 50%, 37%, and 9%, respectively, of patients receiving ENBREL[®], compared to 13%, 4%, and 1%, respectively, of patients receiving placebo. Similar responses were seen in patients with each of the subtypes of psoriatic arthritis, although few patients were enrolled with the arthritis mutilans and ankylosing spondylitis-like subtypes. The results of this study were similar to those seen in an earlier single-center, randomized, placebo-controlled study of 60 patients with psoriatic arthritis.

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

Radiographic Response

Radiographic changes were also assessed in the psoriatic arthritis study. Radiographs of hands and wrists were obtained at baseline and months 6, 12, and 24. A modified Total Sharp Score (TSS), which included distal interphalangeal joints (i.e., not identical to the modified TSS used for rheumatoid arthritis) was used by readers blinded to treatment group to assess the radiographs. Some radiographic features specific to psoriatic arthritis (e.g., pencil-and-cup

deformity, joint space widening, gross osteolysis and ankylosis) were included in the scoring system, but others (e.g., phalangeal tuft resorption, juxta-articular and shaft periostitis) were not.

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

Physical Function Response

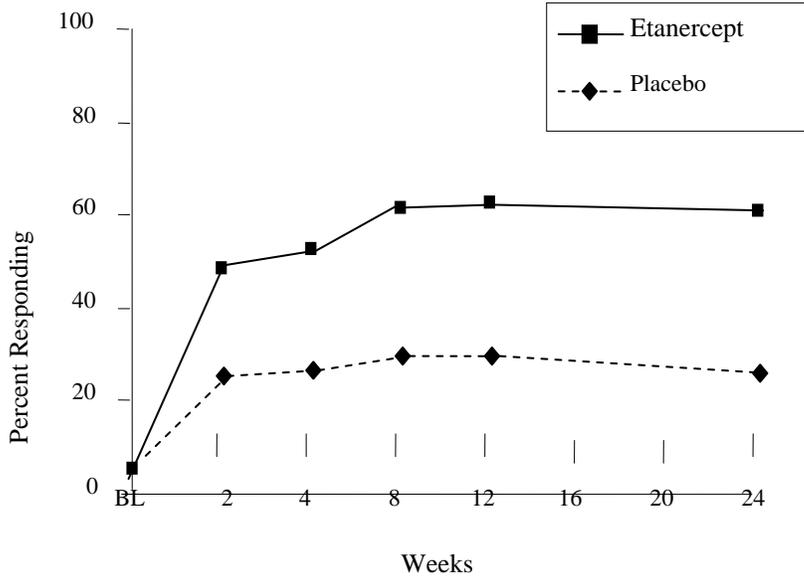
In the psoriatic arthritis study, physical function and disability were assessed using the HAQ Disability Index (HAQ-DI)¹ and the SF-36² Health Survey. Patients treated with 25 mg ENBREL[®] twice weekly showed greater improvement from baseline in the HAQ-DI score (mean decreases of 54% at both months 3 and 6) in comparison to placebo (mean decreases of 6% at both months 3 and 6) ($p < 0.001$). At months 3 and 6, patients treated with ENBREL[®] showed greater improvement from baseline in the SF-36 physical component summary score compared to patients treated with placebo, and no worsening in the SF-36 mental component summary score. Improvements in physical function and disability measures were maintained for up to 2 years through the open-label portion of the study.

Ankylosing Spondylitis

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

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

Figure 2: ASAS 20 Responses in Ankylosing Spondylitis



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

Table 7:
Components of Ankylosing Spondylitis Disease Activity

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

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

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

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

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

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

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

Plaque Psoriasis

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

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

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

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

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

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

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

Table 8: Study I Outcomes at 3 and 6 Months

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

6 Months				
PASI 75 n (%)	55 (33%)	36 (21%)	68 (41%)	90 (54%)

^a p = 0.001 compared with placebo.

^b p < 0.0001 compared with placebo.

Table 9: Study II Outcomes at 3 Months

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

^a p < 0.0001 compared with placebo.

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

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

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

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

Efficacy and safety of ENBREL[®] treatment beyond 12 months has not been adequately evaluated in patients with psoriasis.

INDICATIONS AND USAGE

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

ENBREL[®] is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients ages 2 and older.

ENBREL[®] is indicated for reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with psoriatic arthritis. ENBREL[®] can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone.

ENBREL[®] is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

ENBREL[®] is indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

CONTRAINDICATIONS

ENBREL[®] should not be administered to patients with sepsis or with known hypersensitivity to ENBREL[®] or any of its components.

WARNINGS

Infections

In post-marketing reports, serious infections and sepsis, include fatalities, have been reported with the use of ENBREL[®]. Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their underlying disease, 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 or sepsis. Treatment with ENBREL[®] should not be initiated in patients with active infections, including chronic or localized infections. Physicians should exercise caution when considering the use of ENBREL[®] in patients with a history of recurring infections or with underlying conditions which may predispose patients to infections, such as advanced or poorly controlled diabetes (see **PRECAUTIONS** and **ADVERSE REACTIONS: Infections**).

Cases of tuberculosis have been observed in patients receiving TNF-blocking agents, including ENBREL[®]. Tuberculosis may be caused by reactivation of latent tuberculosis infection or new infection. Data from clinical trials and preclinical studies suggest that the risk of reactivation of latent tuberculosis infection is lower with ENBREL[®] than with TNF-blocking monoclonal antibodies. Nonetheless, postmarketing cases of tuberculosis reactivation have been reported for TNF blockers, including ENBREL[®]. Patients should be evaluated for tuberculosis risk factors and be tested for latent tuberculosis infection. Treatment of latent tuberculosis infections should be initiated prior to therapy with ENBREL[®]. Patients receiving ENBREL[®] should be monitored closely for signs and symptoms of active tuberculosis. The possibility of tuberculosis should be considered, especially in patients who have traveled to countries with a high prevalence of tuberculosis or had close contact with a person with active tuberculosis. All patients treated with ENBREL[®] should have a thorough history taken prior to initiating therapy.

In a 24-week study of concurrent ENBREL[®] and anakinra therapy, the rate of serious infections in the combination arm (7%) was higher than with ENBREL[®] alone (0%). The combination of ENBREL[®] and anakinra did not result in higher ACR response rates compared to ENBREL[®] alone (see **CLINICAL STUDIES: Clinical Response** and **ADVERSE REACTIONS: Infections**). Concurrent therapy with ENBREL[®] and anakinra is not recommended.

Neurologic Events

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. The causal relationship to ENBREL[®] therapy remains unclear. While no clinical trials have been performed evaluating ENBREL[®] therapy in patients with multiple sclerosis, other TNF antagonists administered to patients with multiple sclerosis have been associated with increases in disease activity.^{7, 8} Prescribers should exercise caution in considering the use of ENBREL[®] in patients with preexisting or recent-onset central nervous system demyelinating disorders (see **ADVERSE REACTIONS**).

Hematologic Events

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

Two percent of patients treated concurrently with ENBREL[®] and anakinra developed neutropenia (ANC < 1 x 10⁹/L). While neutropenic, one patient developed cellulitis which recovered with antibiotic therapy.

Malignancies

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, the potential role of TNF-blocking therapy in the development of malignancies is not known (see **ADVERSE REACTIONS: Malignancies**).^{11, 12}

In a randomized, placebo-controlled study of 180 patients with Wegener's granulomatosis where ENBREL[®] was added to standard treatment (including cyclophosphamide, methotrexate, and corticosteroids), patients receiving ENBREL[®] experienced more non-cutaneous solid malignancies than patients receiving placebo (see **ADVERSE REACTIONS: Malignancies**).

The addition of ENBREL[®] to standard treatment was not associated with improved clinical outcomes when compared with standard therapy alone. The use of ENBREL[®] in patients with Wegener's granulomatosis receiving immunosuppressive agents is not recommended. The use of ENBREL[®] in patients receiving concurrent cyclophosphamide therapy is not recommended.

Hepatitis B Virus Reactivation

Use of TNF blockers, including ENBREL[®], has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. 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 prior evidence of HBV infection before initiating TNF blocker therapy. Prescribers should exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. 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. Patients who are carriers of HBV and require treatment with ENBREL[®] should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, consideration should be given to stopping ENBREL[®] and initiating anti-viral therapy with appropriate supportive treatment. The safety of resuming ENBREL[®] therapy after HBV reactivation is controlled is not known. Therefore, prescribers should weigh the risks and benefits when considering resumption of therapy in this situation.

PRECAUTIONS

General

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

Caution: The needle cap on the prefilled syringe and on the SureClick[™] autoinjector contains dry natural rubber (a derivative of latex) which may cause allergic reactions in individuals sensitive to latex.

Information for Patients

Patients or their caregivers should be provided the ENBREL[®] "Patient Information" insert and provided an opportunity to read it and ask questions prior to initiation of therapy. The health care provider should ask the patient questions to determine any risk factors for treatment. Patients developing signs and symptoms of infection should seek medical evaluation immediately.

Latex Sensitivity Allergies

ENBREL[®] is provided as a single-use prefilled syringe, a single-use prefilled SureClick[™] autoinjector, or a multiple-use vial. The patient or caregiver should be informed that the needle cap on the prefilled syringe and on the SureClick[™] autoinjector contains dry natural rubber (a derivative of latex), which should not be handled by persons sensitive to latex.

Administration of ENBREL[®]

If a patient or caregiver is to administer ENBREL[®], the patient or caregiver should be instructed in injection techniques and how to measure and administer the correct dose (see the ENBREL[®] (etanercept) “Patient Information” insert). The first injection should be performed under the supervision of a qualified health care professional. The patient’s or caregiver’s ability to inject subcutaneously should be assessed. Patients and caregivers should be instructed in the technique as well as proper syringe and needle disposal, and be cautioned against reuse of needles and syringes. A puncture-resistant container for disposal of needles, syringes, and autoinjectors should be used. If the product is intended for multiple use, additional syringes, needles, and alcohol swabs will be required.

Patients with Heart Failure

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

Immunosuppression

Anti-TNF therapies, including ENBREL[®], affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. 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 impact of treatment with ENBREL[®] on the development and course of malignancies, as well as active and/or chronic infections, is not fully understood (see **WARNINGS: Malignancies, ADVERSE REACTIONS: Infections, and Malignancies**). The safety and efficacy of ENBREL[®] in patients with immunosuppression or chronic infections have not been evaluated.

Immunizations

Most psoriatic arthritis patients receiving ENBREL[®] were able to mount effective B-cell immune responses 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[®]. The clinical significance of this is unknown. Patients receiving ENBREL[®] may receive concurrent vaccinations, except for live vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving ENBREL[®] (see **PRECAUTIONS: Immunosuppression**).

It is recommended that JIA patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating ENBREL[®] therapy. Patients with a significant exposure to varicella virus should temporarily discontinue ENBREL[®] therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

Autoimmunity

Treatment with ENBREL[®] may result in the formation of autoantibodies (see **ADVERSE REACTIONS: Autoantibodies**) and, rarely, in the development of a lupus-like syndrome or autoimmune hepatitis (see **ADVERSE REACTIONS: Adverse Reaction Information from Spontaneous Reports**), which may resolve following withdrawal of ENBREL[®]. If a patient develops symptoms and findings suggestive of a lupus-like syndrome or autoimmune hepatitis following treatment with ENBREL[®], treatment should be discontinued and the patient should be carefully evaluated.

Drug Interactions

Specific drug interaction studies have not been conducted with ENBREL[®]. However, it was observed that the pharmacokinetics of ENBREL[®] was unaltered by concomitant methotrexate in rheumatoid arthritis patients.

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

In a study of patients with Wegener's granulomatosis, the addition of ENBREL[®] to standard therapy (including cyclophosphamide) was associated with a higher incidence of non-cutaneous solid malignancies. The use of ENBREL[®] in patients receiving concurrent cyclophosphamide therapy is not recommended (see **WARNINGS: Malignancies** and **ADVERSE REACTIONS: Malignancies**).

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

Pregnancy (Category B)

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

Pregnancy Registry: To monitor outcomes of pregnant women exposed to ENBREL[®], a pregnancy registry has been established. Physicians are encouraged to register patients by calling 1-877-311-8972.

Nursing Mothers

It is not known whether ENBREL[®] is excreted in human milk or absorbed systemically after ingestion. 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 to discontinue the drug.

Geriatric Use

A total of 480 RA patients and 89 plaque psoriasis patients ages 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. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

Pediatric Use

ENBREL[®] is indicated for treatment of polyarticular-course juvenile idiopathic arthritis in patients ages 2 and older. For issues relevant to pediatric patients, in addition to other sections of the label, see also **WARNINGS; PRECAUTIONS: Immunizations;** and **ADVERSE REACTIONS: Adverse Reactions in Patients with JIA.** ENBREL[®] has not been studied in children < 2 years of age.

The safety and efficacy of ENBREL[®] in pediatric patients with plaque psoriasis have not been studied.

ADVERSE REACTIONS

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

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

Injection Site Reactions

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

Infections

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

In placebo-controlled trials in RA, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis no increase in the incidence of serious infections was observed (approximately 1% in both placebo- and ENBREL[®]-treated groups). In all clinical trials in RA, serious infections experienced by patients have included: pyelonephritis, bronchitis, septic arthritis, abdominal abscess, cellulitis, osteomyelitis, wound infection, pneumonia, foot abscess, leg ulcer, diarrhea, sinusitis, and sepsis. The rate of serious infections has not increased in open-label extension trials and is similar to that observed in ENBREL[®]- and placebo-treated patients from controlled trials. Serious infections, including sepsis and death, have also been reported during post-marketing use of ENBREL[®]. Some have occurred within a few weeks after initiating treatment with ENBREL[®]. Many of the patients had underlying conditions (e.g., diabetes, congestive heart failure, history of active or chronic infections) in addition to their rheumatoid

arthritis (see **WARNINGS**). Data from a sepsis clinical trial not specifically in patients with RA suggest that ENBREL[®] treatment may increase mortality in patients with established sepsis.⁹

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

In post-marketing experience in rheumatologic indications, infections have been observed with various pathogens including viral, bacterial, fungal, and protozoal organisms. Infections have been noted in all organ systems and have been reported in patients receiving ENBREL[®] alone or in combination with immunosuppressive agents.

In clinical trials in plaque psoriasis, serious infections experienced by ENBREL[®]-treated patients have included: cellulitis, gastroenteritis, pneumonia, abscess, and osteomyelitis.

In global clinical studies of 20,070 patients (28,308 patient-years of therapy), tuberculosis was observed in approximately 0.01% of patients. In 15,438 patients (23,524 patient-years of therapy) from clinical studies in the US and Canada, tuberculosis was observed in approximately 0.007% of patients. These studies include reports of pulmonary and extra-pulmonary tuberculosis (see **WARNINGS**).

Malignancies

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.¹⁰ 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^{11, 12} (see **WARNINGS: Malignancies**). Sixty-seven malignancies, other than lymphoma, were observed. Of these, the most common malignancies were colon, breast, lung, and prostate, which were similar in type and number to what would be expected in the general population.¹⁰ Analysis of the cancer rates at 6 month intervals suggest constant rates over five years of observation.

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

Among 89 patients with Wegener's granulomatosis receiving ENBREL[®] in a randomized, placebo-controlled trial, 5 experienced a variety of non-cutaneous solid malignancies compared with none receiving placebo (see **WARNINGS: Malignancies**).

Immunogenicity

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

The data reflect the percentage of patients whose test results were considered positive for antibodies to ENBREL[®] in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of any antibody positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ENBREL[®] with the incidence of antibodies to other products may be misleading.

Autoantibodies

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

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

Other Adverse Reactions

Table 10 summarizes 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 relevant events from Study III. In placebo-controlled plaque psoriasis trials, the percentages of patients reporting injection site reactions were lower in

the placebo dose group (6.4%) than in the ENBREL[®] dose groups (15.5%) in Studies I and II. Otherwise, the percentages of patients reporting adverse events in the 50 mg twice a week dose group were similar to those observed in the 25 mg twice a week dose group or placebo group. In psoriasis Study I, there were no serious adverse events of worsening psoriasis following withdrawal of study drug. However, adverse events of worsening psoriasis including three serious adverse events were observed during the course of the clinical trials. Urticaria and non-infectious hepatitis were observed in a small number of patients and angioedema was observed in one patient in clinical studies. Urticaria and angioedema have also been reported in spontaneous post-marketing reports. Adverse events in psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis trials were similar to those reported in RA clinical trials.

Table 10:
Percent of RA Patients Reporting Adverse Events
in Controlled Clinical Trials*

Event	Placebo Controlled		Active Controlled (Study III)	
	Percent of patients		Percent of patients	
	Placebo [†] (N = 152)	ENBREL [®] (N = 349)	MTX (N = 217)	ENBREL [®] (N = 415)
Injection site reaction	10	37	7	34
Infection (total)**	32	35	72	64
Non-upper respiratory infection (non-URI)**	32	38	60	51
Upper respiratory infection (URI)**	16	29	39	31
Headache	13	17	27	24
Nausea	10	9	29	15
Rhinitis	8	12	14	16
Dizziness	5	7	11	8
Pharyngitis	5	7	9	6
Cough	3	6	6	5
Asthenia	3	5	12	11
Abdominal pain	3	5	10	10
Rash	3	5	23	14
Peripheral edema	3	2	4	8
Respiratory disorder	1	5	NA	NA
Dyspepsia	1	4	10	11
Sinusitis	2	3	3	5
Vomiting	-	3	8	5
Mouth ulcer	1	2	14	6
Alopecia	1	1	12	6
Pneumonitis (“MTX lung”)	-	-	2	0

* Includes data from the 6-month study in which patients received concurrent MTX therapy.

[†] The duration of exposure for patients receiving placebo was less than the ENBREL[®]-treated patients.

** Infection (total) includes data from all three placebo-controlled trials. Non-URI and URI include data only from the two placebo-controlled trials where infections were collected separately from adverse events (placebo N = 110, ENBREL[®] N = 213).

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

Cardiovascular:	heart failure, myocardial infarction, myocardial ischemia, hypertension, hypotension, deep vein thrombosis, thrombophlebitis
Digestive:	cholecystitis, pancreatitis, gastrointestinal hemorrhage, appendicitis
Hematologic/Lymphatic:	lymphadenopathy
Musculoskeletal:	bursitis, polymyositis
Nervous:	cerebral ischemia, depression, multiple sclerosis (see WARNINGS: Neurologic Events)
Respiratory:	dyspnea, pulmonary embolism, sarcoidosis
Skin:	worsening psoriasis
Urogenital:	membranous glomerulonephropathy, kidney calculus

In a randomized controlled trial in which 51 patients with RA received ENBREL[®] 50 mg twice weekly and 25 patients received ENBREL[®] 25 mg twice weekly, the following serious adverse events were observed in the 50 mg twice weekly arm: gastrointestinal bleeding, normal pressure hydrocephalus, seizure, and stroke. No serious adverse events were observed in the 25 mg arm.

Adverse Reactions in Patients with JIA

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

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

Forty-three of 69 (62%) children with JIA experienced an infection while receiving ENBREL[®] during three months of study (part 1 open-label), and the frequency and severity of infections was similar in 58 patients completing 12 months of open-label extension therapy. The types of

infections reported in JIA patients were generally mild and consistent with those commonly seen in outpatient pediatric populations. Two JIA patients developed varicella infection and signs and symptoms of aseptic meningitis which resolved without sequelae.

The following adverse events were reported more commonly in 69 JIA patients receiving 3 months of ENBREL[®] compared to the 349 adult RA patients in placebo-controlled trials. These included headache (19% of patients, 1.7 events per patient-year), nausea (9%, 1.0 events per patient-year), abdominal pain (19%, 0.74 events per patient-year), and vomiting (13%, 0.74 events per patient-year).

In open-label clinical studies of children with JIA, adverse events reported in those aged 2 to 4 years were similar to adverse events reported in older children.

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

Patients with Heart Failure

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

Adverse Reaction Information from Spontaneous Reports

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

Additional adverse events are listed by body system below:

Body as a whole:	angioedema, fatigue, fever, flu syndrome, generalized pain, weight gain
Cardiovascular:	chest pain, vasodilation (flushing), new-onset congestive heart failure (see PRECAUTIONS: Patients with Heart Failure)
Digestive:	altered sense of taste, anorexia, diarrhea, dry mouth, intestinal perforation

Hematologic/Lymphatic:	adenopathy, anemia, aplastic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia (see WARNINGS)
Hepatobiliary:	autoimmune hepatitis
Musculoskeletal:	joint pain, lupus-like syndrome with manifestations including rash consistent with subacute or discoid lupus
Nervous:	paresthesias, stroke, seizures and central nervous system events suggestive of multiple sclerosis or isolated demyelinating conditions such as transverse myelitis or optic neuritis (see WARNINGS)
Ocular:	dry eyes, ocular inflammation
Respiratory:	dyspnea, interstitial lung disease, pulmonary disease, worsening of prior lung disorder
Skin:	cutaneous vasculitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, pruritus, subcutaneous nodules, urticaria

OVERDOSAGE

The maximum tolerated dose of ENBREL[®] has not been established in humans. Toxicology studies have been performed in monkeys at doses up to 30 times the human dose with no evidence of dose-limiting toxicities. No dose-limiting toxicities have been observed during clinical trials of ENBREL[®]. Single IV doses up to 60 mg/m² have been administered to healthy volunteers in an endotoxemia study without evidence of dose-limiting toxicities.

DOSAGE AND ADMINISTRATION

General

A 50 mg dose should be given as one subcutaneous (SC) injection using either a 50 mg single-use prefilled syringe or a single-use prefilled SureClick[™] autoinjector. A 50 mg dose can also be given as two 25 mg SC injections using 25 mg single-use prefilled syringes or multiple-use vials.

When administering ENBREL[®] as two injections in adults or children, the injections should be given either on the same day or 3 or 4 days apart (see **CLINICAL STUDIES**).

Sites for injection (thigh, abdomen, or upper arm) should be rotated. Never inject into areas where the skin is tender, bruised, red, or hard. See the ENBREL[®] (etanercept) “Patient Information” insert for detailed information on injection site selection and dose administration.

Adult RA, AS, and Psoriatic Arthritis Patients

The recommended dose of ENBREL[®] for adult patients with rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis is 50 mg per week. Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics may be continued during treatment with ENBREL[®]. Based on a study of 50 mg ENBREL[®] twice weekly in patients with RA that suggested higher incidence of adverse reactions but similar ACR response rates, doses higher than 50 mg per week are not recommended (see **ADVERSE REACTIONS**).

Adult Plaque Psoriasis Patients

The recommended starting dose of ENBREL[®] for adult patients is a 50 mg dose given twice weekly (administered 3 or 4 days apart) for 3 months followed by a reduction to a maintenance dose of 50 mg per week (see **CLINICAL STUDIES**).

Starting doses of ENBREL[®] of 25 mg or 50 mg per week were also shown to be efficacious. The proportion of responders were related to ENBREL[®] dosage (see **CLINICAL STUDIES**).

JIA Patients

The recommended dose of ENBREL[®] for pediatric patients ages 2 to 17 years with active polyarticular-course JIA is 0.8 mg/kg per week (up to a maximum of 50 mg per week). The 25 mg prefilled syringe is not recommended for pediatric patients weighing less than 31 kg (68 pounds). The 50 mg prefilled syringe or SureClick[™] autoinjector may be used for pediatric patients weighing 63 kg (138 pounds) or more. Glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), or analgesics may be continued during treatment with ENBREL[®]. Concurrent use with methotrexate and higher doses of ENBREL[®] have not been studied in pediatric patients.

Preparation of ENBREL[®]

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

The ENBREL[®] (etanercept) “Patient Information” insert contains more detailed instructions on the preparation of ENBREL[®].

Preparation of ENBREL[®] Using the Single-use Prefilled Syringe:

Before injection, ENBREL[®] may be allowed to reach room temperature (approximately 15 to 30 minutes). DO NOT remove the needle cover while allowing the prefilled syringe to reach room temperature.

Prior to administration, visually inspect the solution for particulate matter and discoloration. There may be small white particles of protein in the solution. This is not unusual for proteinaceous solutions. The solution should not be used if discolored or cloudy, or if foreign particulate matter is present. Check to see if the amount of liquid in the prefilled syringe falls

between the two purple fill level indicator lines on the syringe. If the syringe does not have the right amount of liquid, DO NOT USE THAT SYRINGE.

Preparation of ENBREL[®] Using the Single-use Prefilled SureClick[™] Autoinjector:

Before injection, ENBREL[®] may be allowed to reach room temperature (approximately 15 to 30 minutes). DO NOT remove the needle shield while allowing the SureClick[™] autoinjector to reach room temperature.

Prior to administration, visually inspect the solution for particulate matter and discoloration. There may be small white particles of protein in the solution. This is not unusual for proteinaceous solutions. The solution should not be used if discolored or cloudy, or if foreign particulate matter is present.

Preparation of ENBREL[®] Using the Multiple-use Vial:

ENBREL[®] should be reconstituted aseptically with 1 mL of the supplied Sterile Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol) giving a solution of 1.0 mL containing 25 mg of ENBREL[®].

A vial adapter is supplied for use when reconstituting the lyophilized powder. However, the vial adapter should not be used if multiple doses are going to be withdrawn from the vial. If the vial will be used for multiple doses, a 25-gauge needle should be used for reconstituting and withdrawing ENBREL[®], and the supplied “Mixing Date:” sticker should be attached to the vial and the date of reconstitution entered. Reconstitution with the supplied BWFI, using a 25-gauge needle, yields a preserved, multiple-use solution that must be used within 14 days.

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

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

Generally, dissolution of ENBREL[®] takes less than 10 minutes. Visually inspect the solution for particulate matter and discoloration prior to administration. The solution should not be used if discolored or cloudy, or if particulate matter remains.

Withdraw the correct dose of reconstituted solution into the syringe. Some foam or bubbles may remain in the vial. Remove the syringe from the vial adapter or remove the 25-gauge needle from the syringe. Attach a 27-gauge needle to inject ENBREL[®].

The contents of one vial of ENBREL[®] solution should not be mixed with, or transferred into, the contents of another vial of ENBREL[®]. No other medications should be added to solutions

containing ENBREL[®], and do not reconstitute ENBREL[®] with other diluents. Do not filter reconstituted solution during preparation or administration.

Reconstitution with the supplied BWFI, using a 25-gauge needle, yields a preserved, multiple-use solution that must be used within 14 days. Discard reconstituted solution after 14 days. **PRODUCT STABILITY AND STERILITY CANNOT BE ASSURED AFTER 14 DAYS.**

Storage and Stability

ENBREL[®] Single-use Prefilled Syringe and ENBREL[®] Single-use Prefilled SureClick[™] Autoinjector: Do not use ENBREL[®] beyond the expiration date stamped on the carton or barrel label. ENBREL[®] must be refrigerated at 2° to 8°C (36° to 46°F). **DO NOT FREEZE.** Keep the product in the original carton to protect from light until the time of use. Do not shake.

ENBREL[®] Multiple-use Vial: Do not use a dose tray beyond the expiration date stamped on the carton, dose tray label, vial label, or diluent syringe label. The dose tray containing ENBREL[®] (sterile powder) must be refrigerated at 2° to 8°C (36° to 46°F). **DO NOT FREEZE.**

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

HOW SUPPLIED

Each ENBREL[®] single-use prefilled syringe and ENBREL[®] single-use prefilled SureClick[™] autoinjector contains 50 mg/mL of etanercept in a single-dose syringe with a 27-gauge, ½-inch needle.

25 mg single-use prefilled syringe	Carton of 4	NDC 58406-455-04
50 mg single-use prefilled syringe	Carton of 4	NDC 58406-435-04
50 mg single-use prefilled SureClick [™] autoinjector	Carton of 4	NDC 58406-445-04

ENBREL[®] multiple-use vial is supplied in a carton containing four dose trays. Each dose tray contains one 25 mg vial of etanercept, one diluent syringe (1 mL Sterile Bacteriostatic Water for Injection, USP, containing 0.9% benzyl alcohol), one 27-gauge ½-inch needle, one vial adapter, one plunger, and two alcohol swabs. Each carton contains four “Mixing Date:” stickers.

25 mg multiple-use vial	Carton of 4	NDC 58406-425-34
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Administration of one 50 mg ENBREL[®] prefilled syringe or one ENBREL[®] SureClick[™] autoinjector provides a dose equivalent to two 25 mg ENBREL[®] prefilled syringes or two multiple-use vials of lyophilized ENBREL[®], when vials are reconstituted and administered as recommended.

Rx Only

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