Cross-Discipline Team Leader Review

Date	October 11, 2016
From	Snezana Trajkovic, MD
Subject	Cross-Discipline Team Leader Review
BLA # **Supplement#**	103795 5552
Applicant	Amgen Inc.
Date of Submission	January 5, 2016
PDUFA Goal Date	November 4, 2016
Proprietary Name / **Established (USAN) names**	Enbrel/ etanercept
Dosage forms / Strength	Solution for subcutaneous injection
Proposed Indication(s)	Treatment of pediatric patients ages 4 to 17 years with severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Recommended:	Approval

1. Introduction

Etanercept (Enbrel®) injection for subcutaneous use is a marketed biologic product for which the applicant seeks approval in an efficacy supplement for the new indication of treatment of severe psoriasis in pediatric patients 4 to 17 years of age. The proposed dose and dosing regimen for etanercept is a subcutaneous injection of 0.8 mg/kg once weekly (up to a maximum of dose of 50 mg per week). Etanercept is supplied as a 50mg solution in a single-use prefilled syringe, 50mg solution in a single-use prefilled SureClick autoinjector, 25mg solution in a single-use prefilled syringe and as a 25mg lyophilized powder multiple-use vial for reconstitution.

Etanercept is a dimeric soluble form of the p75 receptor that can bind to two tumor necrosis factor (TNF) molecules and inhibit activity of TNF, a human cytokine involved in inflammatory and immune responses. Etanercept inhibits binding of both TNFα and TNFβ to the cell surface, rendering TNF biologically inactive.

Etanercept was initially licensed in 1998 for the reduction of signs and symptoms of moderate to severely active rheumatoid arthritis in patients who have had an inadequate response to one or more disease-modifying antirheumatic drugs. Approval of additional supplements expanded the indication to include:

- Reducing signs and symptoms of moderately to severely active polyarticular course juvenile idiopathic arthritis (JIA) in patients ages 2 and older (1999).

- 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 treatments with a disease modifying antirheumatic drug (2000)
- Reducing signs and symptoms of active arthritis in patients with psoriatic arthritis (PsA) (2002)
- Inhibiting the progression of structural damage of active arthritis in patients with psoriatic arthritis (2003)
- Reducing signs and symptoms in patients with active ankylosing spondylitis (AS)(2003)
- Improving physical function in rheumatoid arthritis (2003)
- Treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis (PsO) who are candidates for systemic therapy or phototherapy (2004)

In 2008, etanercept received an approval in European Union to extend the psoriasis indication to include pediatric patients ages 8 to 17 years and in 2011, etanercept received approval to lower the minimum age to 6 years.

This memo summarized the findings of the multidisciplinary review team and provides the rationale for my recommended action.

2. Background

On April 30, 2004 etanercept was licensed for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis (PsO) who are candidates for systemic therapy or phototherapy. The 2004 license supplement which included the indication for adult plaque psoriasis did not contain data on the use of etanercept in children, and the Agency recommended that the applicant conduct a placebo-controlled study to determine safety and efficacy in pediatric subjects with plaque psoriasis. The Agency approval letter dated April 30, 2004 defined a pediatric post-marketing commitment (PMC) 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.

In support of fulfillment of the PMC, on September 26, 2007 the applicant submitted an efficacy supplement (S /5350) containing a clinical study report entitled "Placebo-controlled Multicenter Study with Etanercept to Determine Safety and Efficacy in Pediatric Subjects with Plaque Psoriasis (PEDS)" (Study Number 20030211). The efficacy supplement was presented at the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) meeting on June 18, 2008.

The DODAC members recommended an approval of Enbrel for treatment of pediatric patients with psoriasis ages 4 to 17 years.

On July 24, 2008 the Agency issued a complete response (b) (4) . The following deficiencies were listed:

(b) (4)

(b) (4)

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On June 16, 2010 the Agency issued a letter stating that the pediatric PMC had been fulfilled.

As a postmarketing requirement (PMR), in September 2011 the FDA required all sponsors of TNF-α blockers to perform enhanced pharmacovigilance (ePV) for malignancy in pediatric and young adult patients 30 years of age and younger, and to report the findings annually. Enhanced PV starts with a spontaneous report and requires the sponsors to attempt to gather ePV defined elements of the cases if they are lacking. The Office of Surveillance and Epidemiology reviews these results and provides a high-level summary of the sponsors' data, as well as an independent assessment of malignancies in pediatric and young adult patients, to monitor this safety concern. The age group, 30 years and younger, was chosen to enhance signal detection, due to the lower frequency of cancer in the general population in this age group, relative to older groups.

A pre-sBLA meeting was held on September 30, 2015 during which content and format of current sBLA (S/5552) submission were discussed.

3. CMC/Device

No new product quality data were included in this efficacy supplement. The marketed presentations will support the proposed dosing.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were included in this efficacy supplement.

There are no outstanding pharmacology/toxicology issues that would preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

In their efficacy supplement S/5350 submitted in 2007, the applicant submitted clinical pharmacology information associated with Study 20030211. Clinical pharmacology information was reviewed by Clinical Pharmacology/Biopharmaceutics reviewers, Abimbola Adebowale, Ph.D. and Jang-Ik Lee, Pharm.D., Ph.D., who found it acceptable to support the supplement approval. Dr. Adebowale found the following: "*The steady-state trough serum etanercept concentrations in patients with pediatric psoriasis were comparable to those seen in adult patients with psoriasis treated with Enbrel 25mg twice weekly. In addition, these steady-state trough serum etanercept concentrations in patients with pediatric psoriasis were comparable to those seen in patients with juvenile rheumatoid arthritis (JRA) (4 to 17 years old) who were administered 0.4 mg/kg of Enbrel twice weekly for up to 18 weeks.*"

For the treatment of moderate to severe psoriasis in children, it is intended to be administered by subcutaneous injection at 0.8 mg/kg once weekly by subcutaneous injection, up to a maximum of dose of 50 mg per week, which is equivalent to the currently approved etanercept dosing regimen in patients with juvenile idiopathic arthritis (JIA). Accordingly, the recommended etanercept presentation for pediatric patients who weigh less than 138 pounds and require weight-based dosing is 25 mg multiple-use vial. For pediatric patients who weigh 138 pounds or more and require a fixed dose of 50 mg per week, the recommended etanercept presentations are 50 mg single-use prefilled syringe or 50 mg single-use prefilled SureClick autoinjector.

The Clinical Pharmacology/Biopharmaceutics reviewer, Jie Wang, Ph.D., reviewed clinical pharmacology data submitted in this efficacy supplement. His review focused mainly on the immunogenicity impact on PK and efficacy from Studies 20030211 and 20050111 as this information was not included in the supplement S/5350.

In Studies 20030211 and 20050111, a total of 210 subjects received at least 1 dose of etanercept of whom 208 subjects had serum samples available for immunogenicity testing. Immunogenicity evaluation showed that approximately 10% (20/208) of subjects developed

antibodies to etanercept by Week 48 in Study 20030211 and approximately 16% (33/208) of subjects developed antibodies to etanercept through 6 years of treatment in combined Studies 20030211 and 20050111. None of the ADAs were reported as neutralizing (NAb). In his review, Dr. Wang also noted the following: "*The OBP review team has determined that the immunogenicity assays were not appropriately validated for testing of the pediatric PsO patient population (Internal Wrap-up Meeting, August 30, 2016). The OBP review team also pointed out that it may not be feasible to re-test the immunogenicity samples using improved assays because the pediatric PsO clinical trials were conducted more than 10 years ago. Enbrel has been approved for multiple indications including JIA in patients aged 2 years or older; and, to our knowledge, development of antibodies to etanercept has not been reported as a clinical concern. The clinical studies in pediatric PsO patients in the current supplement also did not show that ADA development was associated with a clinical impact on PK or efficacy (see Section 2.2.2 of this review). We also note that the immunogenicity incidence in pediatric PsO patients is numerically higher than that reported in the adult PSO patients, which is somewhat reassuring that the lack of appropriate assay validation does not appear to have impeded the ability of the assay to detect ADA. Given these factors, we would recommend to use the currently available clinical data to inform the immunogenicity section of the label for the pediatric PsO indication, although we acknowledge the limitations of the immunogenicity assays and agree that the reported incidence of ADA and NAb may not be accurate."*

The presence of ADA did not appear to be associated with decreased etanercept concentrations or reduced PASI 75 response rate at Week 12 in Study 20030211. However, definitive conclusion on the impact of immunogenicity on PK or efficacy could not be made due to a small number of ADA positive subjects.

The Clinical Pharmacology/Biopharmaceutics reviewer, Jie Wang, Ph.D., found that the applicant met the requirements for approval from a clinical pharmacology/biopharmaceutics perspective, and recommended an approval.

6. Clinical Microbiology

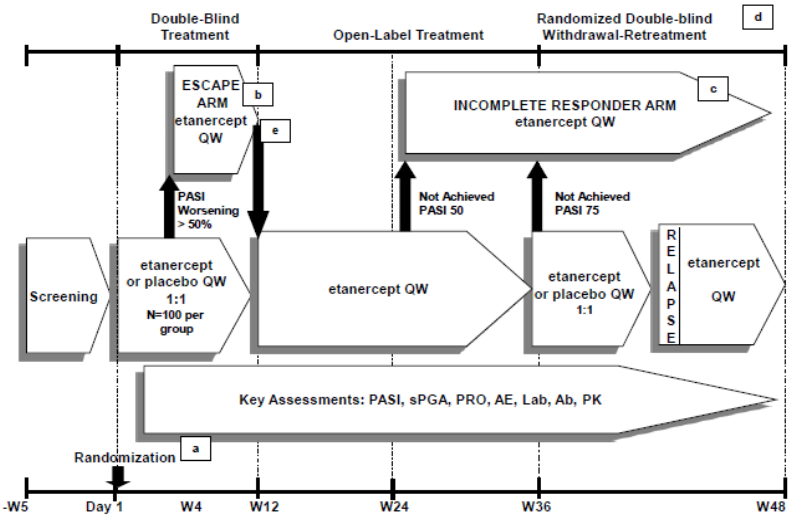
Not applicable.

7. Clinical/Statistical- Efficacy

The applicant submitted data from a single pivotal trial 20030211 to establish the effectiveness of their product in the treatment of moderate to severe psoriasis. The trial was randomized, double-blind and placebo-controlled, with parallel groups and consisted of 3 phases. In the first phase (period A), subjects received either etanercept 0.8mg/kg (up to maximum dose of 50mg) once weekly (QW) or placebo. 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 and receive open-label etanercept QW through Week 12. In the second phase

(period B), all subjects, including those in the escape arm, received open-label treatment with etanercept QW through the Week 36. The third phase (period C) was a double-blind withdrawal-retreatment period in which subjects who achieved a PASI 75 response at Week 36 were re-randomized to placebo or etanercept QW.

Schematic for Study 20030211 is presented below:



Ab = anti-etanercept antibodies; AE = adverse events; Lab = laboratory; PASI = Psoriasis Area and Severity Index; PK = pharmacokinetics; PRO = patient-reported outcomes; QW = once weekly; sPGA = static Physician's Global Assessment of Psoriasis

[a] Subjects were considered to be enrolled after the subject was determined to be eligible for the study and once a randomization call was made into the interactive voice response system. Randomization was stratified based on age group (4 to 11 vs 12 to 17 years of age). Baseline assessments and the first dose administration were to be done on the same day. If unavoidable, randomization could have been done 1 business day earlier.

[b] Subjects who had a disease worsening on or after week 4 through 12 were eligible to receive open-label etanercept treatment.

[c] Subjects who did not achieve a PASI 50 response at week 24 or did not achieve a PASI 75 response at week 36 were eligible to enter the incomplete-responder arm.

[d] Subjects who achieved a PASI 75 response at week 36, not including those already in the incomplete-responder arm, were to be randomized to the active or placebo arm, and resumed open-label treatment upon disease relapse.

[e] Etanercept 0.8 mg/kg (up to an intended dose of 50 mg) was to be administered QW using 1 or 2 vials.

Source: Figure 7-1 of Study 20030211

Enrolled subjects were 4 to 17 years of age, with moderate-to-severe plaque psoriasis defined as a Static Physician's Global Assessment of Psoriasis (sPGA) score ≥ 3 (moderate); body surface area involvement (BSA) ≥ 10% and a psoriasis area-and-severity index (PASI) score ≥ 12. Subject must have been receiving treatment at the time of screening; treated in the past with phototherapy or systemic psoriasis therapy; or considered poorly controlled with topical psoriasis therapy. The time point for efficacy evaluation was at Week 12. The primary efficacy endpoint was the proportion of subjects achieving PASI 75 response rate defined as at least a 75% reduction in Psoriasis Area and Severity Index (PASI) score from baseline. Subjects were stratified into 2 groups at randomization: children (4-12 years old) and adolescents (12 to 17 years old). Within each stratum, subjects were randomized to either etanercept or placebo in a 1:1 ratio.

For systemic products indicated for the treatment of moderate to severe psoriasis, endpoint considered by the Agency as clinically meaningful in evaluation of efficacy should be based on sPGA (the proportion of subjects who achieved sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline). Therefore, co-primary endpoint of PASI 75 and sPGA score were evaluated by the statistical reviewer. The applicant included evaluation of the proportion of subjects who achieved sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline as a second ranked secondary endpoint.
In this trial, etanercept was superior to placebo for the co-primary endpoints of PASI 75 and sPGA score of 0 (clear) or 1 (almost clear) and 2 grade improvement form baseline. The results for the co-primary endpoints are presented in the Table below:

Proportion of Subjects Achieving Co-primary Endpoints of PASI 75 And Response on sPGA at Week 12

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

Source: adapted from Statistical Review and Evaluation sBLA 103795/SN060, Clara Y. Kim, PhD
P-value was calculated using CMH test, stratified by age group. All messing values were imputed as failures.

Ranked secondary endpoints included: 1) PASI 50 response 2) clear/almost clear status on sPGA 3) percent improvement from baseline in Children's Dermatology Life Quality Index (CDLQI) and 4) PASI 90 response.
Because PASI 50 response is not considered a clinically meaningful improvement, this secondary endpoint is not considered for inclusion in labeling.

Secondary endpoint of CDLQI is a patient reported outcome measure that has not be validated prior to use in Phase 3 trial and therefore not eligible for inclusion in labeling.

For the secondary endpoint of PASI 90 response at Week 12, etanercept was superior to placebo (results presented in table below).

Proportion of Subjects Achieving PASI 90 response at Week 12

	Etanercept n=106	**Placebo n=105**
PASI 90 Number of successes (%) p-value	29 (27%)	7 (7%) <0.0001

Source: adapted from Statistical Review and Evaluation sBLA 103795/SN060, Clara Y. Kim, PhD

The reader is referred to the biostatistics reviews by Clara Kim, Ph.D., and Kathleen Fritsch, Ph.D., for detailed review of the pivotal trial and additional analyses, including post hoc explorations of the data and sensitivity analyses.

8. Safety

The applicant submitted data from two Phase 3 trials to establish the safety and effectiveness of their product in the treatment of mild to moderate psoriasis in subjects 4 to 17 years of age. The applicant submitted the data from Study 20030211 and Study 20050111. Study 20030211 was a placebo-controlled study (discussed in section **7. Clinical/Statistical-Efficacy** of this review) and Study 20050111 was an open-label study that included subjects who participated in Study 20030211. Subjects, who achieved $\geq$ PASI 50 response on or after Week 12 and completed Week 48 of Study 20030211, were enrolled in Study 20050111 and were treated with open-label etanercept 0.8 mg/kg (up to 50 mg) administered SQ once weekly for up to 264 weeks or until the subject turned 18 years of age (if later than week 264).

Two hundred ten subjects with moderate to severe psoriasis were exposed to etanercept during the development program. Of these, 199 were exposed for 6 months; 179 were exposed for one year; 125 were exposed to 3 years and; 79 were exposed for 5 years. Overall exposure to etanercept in terms of dose, frequency and duration of dosing, and the target population was adequate for evaluation of safety.

No deaths, opportunistic infections or malignancies were reported during the development program for pediatric psoriasis.

During the Study 20030211, 4 serious adverse events (SAEs) were reported by 3 subjects. All 4 SAE were reported during the open label period (Week 12-36): gastroenteritis and dehydration; lobar pneumonia and; benign ovarian mass. The adverse event of pneumonia was considered by the investigator to be related to etanercept. The adverse events of gastroenteritis and dehydration were considered by the investigator as not related to the study drug however, in the opinion of clinical reviewer Dr. Kettle, the relationship between these SAEs and the study drug administration could not be excluded.
No serious adverse events or serious infections were reported during the 12-week double-blind period or during the randomized withdrawal-retreatment period.

During the open-label Study 20050111, 7subjects reported 8 SAEs: cellulitis, infectious mononucleosis, post-operative intestinal obstruction, osteonecrosis of both hips in a single subject, thyroid cyst, anxiety and, elective abortion. None of these SAEs were considered by the investigator as drug related.
Thirty days post Week 264 or post last dose of Study 20050111, an additional 7 SAEs were reported by 4 subjects: an intentional self injury, brain mass and abnormal behavior in a one subject; hematuria and major depression in one subject; premature separation of placentae and

joint dislocation in one subject each. None of these SAEs were considered by the investigator to be drug related.

During the Study 20030211, 6 subjects discontinued due to AEs. Of these, one subject in the etanercept group discontinued due to bronchospasm during the placebo-controlled period and, 5 subjects on etanercept (atopic dermatitis, worsening of psoriasis, lobar pneumonia, skin infection; and muscle spasm) discontinued during the open label period of the trial.

During the placebo control portion of the Study 20030211, the frequency of commonly-occurring treatment-emergent adverse evets (≥ 5% of subjects) was slightly higher in the etanercept group than the placebo group. Adverse events that occurred in greater than 5% of subjects and at greater frequency in etanercept subjects than placebo are presented in the Table below:

Adverse Events Occurring in Greater than 5% of Subjects and At Greater Frequency in Etanercept Subjects than Placebo (Study 2003011)

Preferred Term	**Etanercept N=106 n (%)**	**Placebo N=105 n (%)**
Number of Subjects Reporting Adverse Events	68 (64)	62 (59)
Upper Respiratory Tract Infection	12 (17)	12 (11)
Headache	14 (13)	12 (12)
Influenza	8 (8)	2 (2)
Gastroenteritis	6 (6)	0 (0)

Source: Applicant's submission. Clinical Study Report 20030211, Section 11.9, page 151

The applicant evaluated the exposure-adjusted rates of AEs that included all subjects who received at least one dose of investigational product during the entire Study 20030211. Although times of exposure to etanercept (E=153.6 subject-years) and placebo (E= 30.1 subject-years) were different, the rates of AEs were similar between two treatment groups (presented below in Table)

Exposure-adjusted Rates of AEs (Study 2003011)

Preferred Term	**Etanercept N=210 (E=153.5) n (r)**	**Placebo N=149 (E= 30.1) n (r)**
Total Number of Events	852 (554.8)	206 (685.3)
Upper Respiratory Tract Infection	83 (54.0)	20 (66.5)
Headache	51 (33.2)	21 (69.9)
Nasopharyngitis	50 (32.6)	12 (39.9)
Pharyngitis Streptococcal	22 (14.3)	1 (3.3)
Influenza	21 (13.7)	5 (16.6)
Vomiting	19 (12.4)	3 (10.0)
Pharyngeal Pain	17 (11.1)	9 (29.9)

Source: Applicant's submission, Clinical Study Report 20030211, Section 11.10, page 154
N = Number of subjects who were randomized and received at least 1 dose of investigational product
E = Total number of exposure years; n = Number of adverse events; r = Exposure-adjusted event rate per 100 subject years (= n / E * 100)

The applicant also provided postmarketing safety information from pediatric patients treated with etanercept in approved and unapproved indications. This information included the reports of enhanced pharmacovigilance (ePV) for malignancy in pediatric and young adult patients 30 years of age and younger. The summary of results of this information is presented below.

As of December 31, 2014, the world-wide cumulative etanercept exposure for patients <18 years of age was 87,869 patient years and in the US was 46,208 patient years.
A total of 47 **deaths** were reported for all indications and one case (suicide) for psoriasis indication.

For **serious infections**, 831 serious cases with 973 serious events were reported for all indications and, 18 serious cases for psoriasis indication.

Opportunistic infections for all indications included the following: pneumocystis jirovecii pneumonia (5 cases); tuberculosis (18 cases); positive tuberculin test (12 cases); primary varicella infections (34 cases); herpes zoster (32 cases) and; aspergillosis (2 cases).
Opportunistic infections for psoriasis indication included the following: primary varicella infection (1 case, confounded by MTX use); herpes zoster (5 cases, confounded by MTX and steroid use); cryptococcosis (1 case); histoplasmosis (1 case); amebiasis (1 case); toxic shock syndrome (1 case).

Enhanced pharmacovigilance for pediatric malignancy for all indications included 21 cases of solid tumor malignancies and 19 cases of lymphoproliferative malignancies.
Enhanced pharmacovigilance for pediatric malignancy for psoriasis indication included no cases of solid tumor malignancies and one case (lymphoma) of lymphoproliferative malignancies.

9. Advisory Committee Meeting

This efficacy supplement was not presented to the Advisory Committee. As discussed in section **2. Background,** efficacy supplement S/5350, containing clinical study report entitled "Placebo-controlled Multicenter Study with Etanercept to Determine Safety and Efficacy in Pediatric Subjects with Plaque Psoriasis (PEDS)" (Study Number 20030211), was presented at the DODAC meeting held on September 26, 2007. The AC members recommended that: benefits of etanercept outweigh the risks for moderate to severe psoriasis in children (votes 7 yes; 5 no; 1 abstain); for approval of etanercept for the treatment of moderate to severe psoriasis in children (votes: 8 yes; 5 no; 0 abstain); in age group 4 to 17 years (votes: 7 yes; 0 no; 6 abstain); to be approved prior to conduct of postmarketing safety study in adults (votes: 9 yes; 3 no; 1 abstain). The AC members advised that the risk-benefit analysis would be patient dependent and would benefit pediatric psoriasis patients with more severe disease.

Current supplement (S/5552) was presented at the Regulatory Briefing held on July 22, 2016. During the meeting, the committee considered the following issues: i) whether the applicant established efficacy of etanercept in the treatment of severe psoriasis ii) has the safety of etanercept been sufficiently characterized iii) did the benefit/risk calculus support the approval of etanercept and iv) if etanercept is to be approved, should it be approved for the population with severe plaque psoriasis or with moderate to severe plaque psoriasis.

The Regulatory Briefing committee members recommended an approval of etanercept for the treatment of pediatric patients 4 to 17 years of age with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

10. Pediatrics

This supplemental application included data from studies of etanercept in the treatment of moderate to severe plaque psoriasis in children 4 to 17 years of age.

On 30 April 2004, the applicant received licensure for the indication of treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. As part of the approval, the applicant agreed to a post-marketing commitment (PMC) to conduct a 48-week, 200 pediatric patients, 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. On September 26, 2007 the applicant submitted the efficacy supplement containing the results from this study. The Agency issued a complete response on July 24, 2008 for this supplement. (b) (4) On June 16, 2010 the Agency issued a letter stating that the above PMC was deemed fulfilled.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications,

new dosage forms, new dosing regimens, or new routes of administrations are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, differed, or inapplicable. Because none of these criteria apply to the current submission, the applicant was not required to submit Initial Pediatric Study Plan (iPSP). This was communicated to the applicant in a letter of September 28, 2015. Current submission does not contain iPSP.

This submission was presented to PeRC on August 16, 2016. No additional studies in pediatric patients with moderate to severe psoriasis were recommended.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

The applicant submitted proposed labeling in the format that complies with the Physicians' Labeling Rule. Professional and patient labeling were reviewed, and negotiations regarding the contents are ongoing at the time of closure of this review.

13. Recommendations/Risk Benefit Assessment

Regulatory action: Approval

This reviewer recommends that etanercept be approved for the treatment of pediatric patients ages 4 to 17 years with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

The clinical reviewer, Roselyn Epps M.D, recommended complete response for the efficacy supplement BLA 103795/S5552. Dr. Epps cited the following deficiencies as basis for her decision:

1. *"Pursuant to 21 CFR 601.3(a)(2), there are insufficient efficacy and safety data in the population with severe psoriasis (6 subjects) to justify the indication of severe plaque psoriasis in patients 4 to 17 years, despite the demonstration of efficacy in the studied population overall"*
2. *"Effects of the use of etanercept on the immune system throughout childhood and the response to recommended vaccines are not known and have not been investigated satisfactorily in this application."*
3. *"In this supplemental application, the immunogenicity assays performed for etanercept antibodies and neutralization antibodies were not validated and therefore inadequate; claims regarding the absence of neutralizing antibodies cannot be made and may result in mislabeling."*

4. *"Safety concerns remain regarding the potential for malignancies and serious infectious morbidities, which appear to outweigh the potential, temporary benefit of this systemic agent in pediatric severe psoriasis patients."*

In order to resolve above stated deficiencies, Dr. Epps recommended that the applicant do the following:

- Conduct an additional study in pediatric patients with severe plaque psoriasis with an adequate number of subjects to achieve statistical power for analysis;
- Modify the anti-etanercept antibody assay and the neutralization assay to achieve validity and reliability, and assess the development of antibodies to etanercept. The antietanercept antibody and neutralization assays need to be specific, sensitive, accurate, tolerant to on-board drug levels, and performed in the indicated population.

I do not concur with Dr. Epps's recommendation of regulatory action for this efficacy supplement or with the recommendations to resolve the deficiencies laid out by Dr. Epps. The following are the reasons for my decision:

1. The guidance for industry, *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products,* discusses the quantity of evidence needed to establish effectiveness for a human drug or biologic product. Section 1 of the guidance addresses situations in which effectiveness of a new use may be extrapolated entirely from existing efficacy studies. The example of a situation in which effectiveness might be extrapolated from efficacy data for another claim or products includes pediatric uses. The guidance states the following:
   "The rule revising the Pediatric Use section of product labeling (21 CFR 201.57(f) (9) (iv)) makes allowance for inclusion of pediatric use information in labeling without controlled clinical trials of the use in children. In such cases, a sponsor must provide other information to support pediatric use, and the Agency must conclude that the course of the disease and the effects of the drug are sufficiently similar in the pediatric and adult populations to permit extrapolation from adult efficacy data to pediatric patients. Evidence that could support a conclusion of similar disease course and similar drug effect in adult and pediatric populations includes evidence of common pathophysiology and natural history of the disease in the adult and pediatric populations, evidence of common drug metabolism and similar concentration-response relationships in each population, and experience with the drug, or other drugs in its therapeutic class, in the disease or condition or related diseases or conditions."

   Psoriasis has common pathophysiology and natural history in the adult and pediatric populations. The applicant provided the evidence of common drug metabolism and similar concentrations-response relationship in each population in the disease or condition. Therefore, it is reasonable to conclude that efficacy of etanercept in the treatment of children with moderate to severe psoriasis may be extrapolated from efficacy in adult population. Therefore, additional efficacy data in pediatric subjects with severe disease, to support the indication of treatment of moderate to severe

psoriasis, is not warranted. See discussion in section **7. Clinical/Statistical-Efficacy** of this review.

2. The effects of etanercept on response to vaccinations were not evaluated in the development program for pediatric psoriasis however; current labeling contains sufficient information to inform providers regarding timing and type of vaccines in pediatric patients on treatment with etanercept. In addition, there is no information indicating that the response to vaccinations would be different in pediatric patients with psoriasis compared to pediatric patients with diseases for which etanercept is approved. For vaccinations, current labeling contains the following recommendations:

   5.8 Immunizations:
   "Live vaccines should not be given concurrently with Enbrel. It is recommended that pediatric patients, if possible, be brought up-to-date with all immunizations in agreement with current immunization guidelines prior to initiating Enbrel therapy"

   7.1 Vaccines
   Most PsA 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 2-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.

3. The immunogenicity assays were not appropriately validated for testing in pediatric subjects with psoriasis. However, the lack of appropriate assay validation did not appear to have impeded the assay's ability to detect ADA. The results of clinical studies in pediatric subjects with psoriasis in this supplement did not show that ADA positivity impacted PK or efficacy of etanercept. Additionally, information regarding immunogenicity of etanercept from multiple approved indications in adults and from pediatric population with JIA, did not show that antibodies to etanercept had clinical impact on safety, efficacy or PK (see discussion regarding immunogenicity assay presented in section **5. Clinical Pharmacology/Biopharmaceutics** of this review).

4. Safety information from conducted studies in subjects with moderate to severe plaque psoriasis did not reveal new safety signals. In addition, information from postmarketing enhanced pharmacovigilance in pediatric patients treated with etanercept did not identify new signals not already addressed in product labeling. Malignancies and serious adverse events are recognized potential risks of treatment with TNF inhibitors. These risks are communicated to healthcare providers and patients in Boxed Warning, Contraindications, Warning and Precautions, Adverse Reactions and Medication Guide sections of current etanercept labeling and allow for making an informed decision regarding appropriate use of the product. The information contained in current labeling

for etanercept supports safe and effective use of this product in children with moderate to severe plaque psoriasis.
The benefit of etanercept treatment in the patient population with moderate to severe psoriasis, for whom no approved effective treatment is currently available, overweighs its potential risks. Due to lack of treatment options, pediatric patients with moderate to severe psoriasis are currently treated with off-label products like methotrexate and cyclosporine for which efficacy and safety in this patient population have not been established. The decision when to use a product with a safety profile that of etanercept should be made by informed healthcare provider and their patients (or caregivers).

In conclusion, it is in this reviewer's opinion that benefits of treatment with etanercept overweigh its risks.

Risk-benefit assessment: The applicant established the efficacy and safety of Enbrel (etanercept) for injection in the treatment of moderate to severe plaque psoriasis in patients 4 years of age and older in one adequate and well-controlled trial and one long-term open-label safety trial, and provided sufficient information in their application to support product labeling.

Postmarketing Risk Evaluation and Management Strategies: Prescription status, routine pharmacovigilance, and professional and patient labeling are adequate risk management measures for the product.

Postmarketing Requirements and Commitments: None

Recommended Comments to Applicant: None

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/s/

SNEZANA TRAJKOVIC
10/11/2016