

Summary Review for Regulatory Action

Date	4 November 2016
From	Jill A Lindstrom, MD FAAD
Subject	Deputy Division Director Summary Review
BLA #	103795
Supplement #	5552
Applicant Name	Immunex Corporation
Date of Submission	5 January 2016
PDUFA Goal Date	4 November 2016
Proprietary Name / Established (USAN) Name	Enbrel etanercept
Dosage Forms / Strength	Injection: 25mg/0.5mL and 50 mg/mL in a single-dose prefilled syringe Injection: 50mg/mL in a single dose prefilled autoinjector For injection: 25mg lyophilized powder in a multiple-dose vial for reconstitution
Proposed Indication(s)	Treatment of pediatric patients ages 4 to 17 years with chronic severe plaque psoriasis who are candidates for systemic therapy of phototherapy
Action:	<i>Approval</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Roselyn E Epps, MD
Statistical Review	Kathleen Fritsch, PhD
Product Quality Review	Peter Adams, PhD
OBP Immunogenicity Assay Review	Brian Janelsins, PhD
CDRH	Jamie Kamon-Brancazio
OPQ DIA/TB-EER	Ephrem Hunde
Clinical Pharmacology Reviews	Jie Wang, PhD; Abimbola Adebawale, PhD
Labeling	Nancy Xu, MD;
Labeling, OBP	Jabril Abdus-Samad, PharmD
CDTL Review	Snezana Trajkovic, MD
OSE/DMEPA	Carlos Mena-Grillasca, RPh
OSE/DPV	Jessica Weintraub, PharmD
OSE/DEPI II	Patty Greene, PharmD
Ethics/OPT	Robert M. Nelson, MD, PhD
Project Management	Matthew White

OND=Office of New Drugs

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DPV=Division of Pharmacovigilance

DEPI= Division of Epidemiology

CDTL=Cross-Discipline Team Leader

OPQ DIA=Office of Pharmaceutical Quality Division of Inspectional Assessment

1. Introduction

Enbrel (etanercept) for subcutaneous injection is a tumor necrosis factor blocker product for which the applicant seeks to supplement the license under Section 351 of the PHS Act and approval under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for the indication of treatment of pediatric patients ages 4 to 17 years with chronic severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Enbrel was initially licensed in 1998 for the treatment of moderately to severely active rheumatoid arthritis. Supplements to the license were approved for treatment of polyarticular juvenile rheumatoid arthritis (now juvenile inflammatory arthritis) in pediatric patients 4 years of age and older in 1999 (extended down to 2 years of age in 2006), psoriatic arthritis in 2002, ankylosing spondylitis in 2003, and chronic moderate to severe plaque psoriasis in adults in 2004. A supplement for moderate to severe plaque psoriasis in children ages 4 to 17 years, submitted in 2007, received a complete response letter in 2008. The current supplement provides additional safety information to support use in pediatric patients ages 4 to 17 years with plaque psoriasis.

This memo summarizes the findings of the multi-disciplinary review team and provides the rationale for my decision.

2. Background

Psoriasis is a chronic inflammatory disease affecting primarily the skin and joints that is characterized by circumscribed erythematous scaly plaques on the skin and substantial impairment of quality of life. Overall prevalence of psoriasis in the US is approximately 2%, and prevalence in childhood and adolescence is reported to be between 0.3% and 2%. An estimated 20% of patients have moderate-to-severe disease, affecting greater than 5 or 10% of the body surface area (BSA) or involving body areas such as the hands and feet. One third of patients have concomitant arthritis. Co-morbidities include depression/suicide, autoimmune disease, cardiovascular disease, metabolic syndrome. The negative impact of psoriasis on quality of life has been found to be comparable or in excess of that with cancer, arthritis, hypertension, heart disease and diabetes, and childhood onset of disease correlates with impaired social development, social withdrawal, sleep problems and substance abuse.

The Guidelines of Care For the Management of Psoriasis and Psoriatic Arthritis, published by the American Academy of Dermatology in 6 parts from 2008 to 2011, recommend, as a general approach for patients with psoriasis without concomitant psoriatic arthritis, treatment with topical products or targeted phototherapy for limited disease, and phototherapy or systemic therapy with drugs or biologic products for extensive disease (>5% BSA involvement). The current therapeutic armamentarium approved or cleared for treatment of adults with moderate to severe disease includes topical therapies (corticosteroids, tazarotene, corticosteroid and vitamin D analog combination products), phototherapy and photochemotherapy (methoxsalen), systemic small molecule drugs (acitretin, apremilast, cyclosporine, methotrexate), and systemic biologic products (adalimumab, etanercept, infliximab, ixekizumab, secukinumab, and ustekinumab). However for children with moderate to severe psoriasis, there are no approved systemic drugs or biologic products; the only approved or cleared therapeutic options are UVB phototherapy, mometasone furoate (a mid-potency topical steroid), tazarotene gel (for patients 12 years and older) and calcipotriene/betamethasone dipropionate ointment (for patients 12 years and older). For children

with BSA involvement of 10% or more, such as the subjects enrolled in the studies conducted to support this supplement, topical treatments and phototherapy may be impractical due to time and expense, or ineffective; thus to treat their disease, patients and healthcare providers may utilize drugs or biologic products not approved for use in children. In this supplement, the applicant provided information from a commercial claims database that found that, of pediatric patients with psoriasis in the database, (b) (4) % had filled a prescription for a systemic treatment considered standard of care for adults and (b) (4) % had filled a prescription for a biologic therapy considered standard of care for adults—presumably healthcare providers relied on literature, anecdotal evidence, expert opinion, or labeling information for other conditions in children, such as juvenile inflammatory arthritis, to make dose and treatment decisions. This data supports the need for approved systemic treatment options, with accompanying labeling, for pediatric patients with psoriasis. Additionally, the Agency heard, through the Patient Focused Drug Development meeting on psoriasis held in March 2016, from pediatric patients who were frustrated because they had to wait until their 18th birthday to receive etanercept, and even developed suicidal thoughts because of the severe adverse psychosocial impacts of psoriasis on their lives. Pediatric dermatologists spoke compellingly, at the meeting and through comments submitted to the docket, of the need for approved systemic treatment options for their pediatric patients with extensive or refractory disease.

In 2004, at the time of approval of supplement 5149 for treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy, the applicant agreed to a postmarketing commitment to conduct Study 20030211, a 48-week trial in 200 pediatric patients to evaluate the safety and efficacy of Enbrel in pediatric patients ages 4 to 17 years of age with chronic plaque psoriasis. Following completion of this study, the applicant submitted a supplemental application (5350) for treatment of moderate to severe plaque psoriasis in pediatric patients 4 to 17 years of age. The application was presented to the Dermatology and Ophthalmology Drug Advisory Committee in June 2008, which recommended approval for the requested indication (see votes and tallies, Section 9, below). However, in July 2008, a Complete Response letter was issued, (b) (4)

The European Union (EU) extended the indication for etanercept to include pediatric patients 8 years and older in 2008, and to 6 years and older in 2011.

3. CMC/Device

No changes to the product or presentations were proposed in this supplemental application.

The claim for a categorical exemption from an environmental assessment was found acceptable.

To assess immunogenicity during the clinical trials, the applicant utilized immunogenicity assays that were not validated, although they were considered acceptable at the time and had been used to support the other indications in the application, including psoriasis in adults (2004) and juvenile inflammatory arthritis in children ages ≥ 2 years of age (2006). The assay cut-point determination would not conform to current FDA, ICH and USP guidance, although this information was not available at the time the cut-point was established. Dr. Janelins, the immunogenicity assay

reviewer, concluded that the incidence of anti-Enbrel antibodies in children with psoriasis has not been accurately determined because the assays are not appropriately validated. He recommended that the applicant develop validated assays for detection of anti-drug antibodies, which could be used in future trials. He did not recommend retesting of banked samples from the completed trials due to the age and quality of the samples.

I acknowledge the limitations of the immunogenicity data as a result of the lack of validation of the assay system. Because i) the immunogenicity assays were acceptable at the time the trials were conducted, ii) the same assays were used for the other indications for which Enbrel is labeled, iii) the Agency has not taken regulatory action to remove the product from the market or require additional safety studies, and iv) similar limitations impact the immunogenicity information for other marketed biologic products, I do not find that the assay limitations or the impact on the immunogenicity data preclude approval. The applicant does not have ongoing trials in pediatric psoriasis. Because development of anti-drug antibodies did not impact the systemic exposure or efficacy of Enbrel in Study 20030211, a post-marketing requirement to conduct an additional clinical trial for the purpose of obtainment of immunogenicity data using a new validated assay (when developed) seems unwarranted. However, should such information be obtained in the future, the applicant should submit a supplemental application to revise product labeling.

Review of the application found no deficiencies in compliance with Quality System Requirements, and no facility inspections for compliance with Quality System Requirements were needed. The manufacturing facilities have no pending or ongoing compliance actions.

There are no outstanding quality issues.

4. Nonclinical Pharmacology/Toxicology

Not applicable.

5. Clinical Pharmacology/Biopharmaceutics

In Study 20030211, which consisted of a 12-week double-blind placebo controlled phase, a 24-week open-label treatment phase, and a 12-week double-blind placebo controlled randomized withdrawal phase among responders only, pharmacokinetic data was obtained at baseline and weeks 12, 24 and 48, and samples for immunogenicity assessment were obtained at baseline and weeks 12 and 48. In Study 20050111, a 264-week open-label extension study, samples for immunogenicity assessment were obtained at baseline and weeks 48, 96, 144, 168 and 264. Pharmacokinetic data demonstrated that systemic exposure in pediatric subjects with psoriasis was comparable to that previously found in adult subjects with psoriasis and pediatric subjects with juvenile rheumatoid arthritis (or JIA). Approximately 10% and 16% of subjects developed anti-drug antibodies by weeks 48 and 264, respectively; none of the antibodies were neutralizing. The presence of antidrug antibodies did not correlate with decreased serum etanercept concentrations or reduced PASI 75 responses, although the numbers of subjects were small. Because of the limitations of the assays, the incidence of binding and neutralizing antibodies may not have been accurately determined.

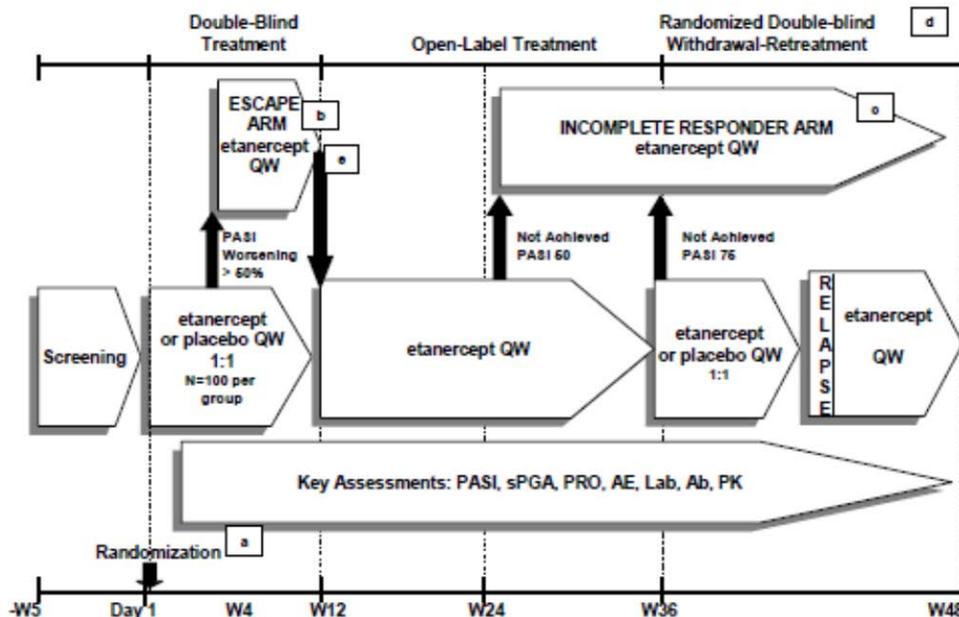
I concur with the conclusions reached by Drs. Wang and Adebowale, the clinical pharmacology/biopharmaceutics reviewers, that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

To establish efficacy, the applicant submitted data from Study 20030211, a multi-center, prospective, randomized, double-blind placebo-controlled study to determine the safety and efficacy of etanercept in the treatment of moderate to severe psoriasis in pediatric subjects. The study, which was conducted in response to a post-marketing commitment, was 48 weeks in duration, had three phases: a 12-week double-blind placebo-controlled phase, a 24-week open-label phase, and a 12-week double-blind randomized withdrawal-retreatment phase. The study design is illustrated in the figure below:



- ^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. Ab = anti-etanercept antibodies; AE = adverse events; Lab = laboratory; PK = pharmacokinetics; PRO = patient reported outcomes; QW = once weekly; sPGA = static physician global assessment

Source: BLA 103795 supplement 5552 Section 5.5.3.1 Clinical Study Report 20030211 p87.

The study enrolled 211 pediatric subjects 4 to 17 years of age with plaque psoriasis. Key inclusion criteria included current or prior treatment with a phototherapy or systemic psoriasis therapy *or* disease which was poorly controlled despite treatment with topical psoriasis therapy; a score on the static Physician Global Assessment (sPGA) scale of at least 3 (moderate); a score on the Psoriasis Area Severity Assessment (PASI) of at least 12; and at least 10% body surface area (BSA) involvement. Subjects were randomized to receive either etanercept 0.8 mg/kg (up to a dose of 50mg) or placebo administered subcutaneously once weekly during the initial phase.

Assessments included PASI and sPGA. The sPGA scale consisted of 6 categories, 0 to 5, which correspond to clear, minimal, mild, moderate, marked and severe, and incorporated assessment of induration or plaque elevation, scaling, and erythema. The sPGA scale, which was comparable to that used in the pivotal studies that enrolled adults, contained an additional category (“marked”) not typical of scales used in psoriasis development programs; thus, subjects with moderate to severe disease were spread across three, rather than two, categories. The primary timepoint was at week 12. The primary endpoint was the proportion of subjects with PASI 75 response, defined as a 75% or greater decrease from baseline in PASI score. Secondary endpoints included PASI 90 response and clear or almost clear status on sPGA. The results on these endpoints, and a calculation for sPGA 0 or 1 with 2 grade improvement (to address erroneous enrollment of a subject with sPGA score of 2) are presented in the table below:

Endpoint	Etanercept N=106	Placebo N=105	P-value
PASI 75	60 (56.6%)	12 (11.4%)	<0.0001
PASI 90	29 (27.4%)	7 (6.7%)	<0.0001
sPGA 0 or 1	56 (52.8%)	14 (13.3%)	<0.0001
sPGA 0 or 1 with 2 grade improvement	55 (51.9%)	14 (13.3%)	<0.0001

Source: derived from Statistical Review and Evaluation; Kathleen Fritsch, PhD; archived 9/1/2016; p9.

Dr. Fritsch, the biostatistics reviewer, noted that the baseline disease severity, based on sPGA score, of the population enrolled in the pediatric studies was comparable to that in the adult studies, and that the mean baseline PASI scores were also similar. Post hoc efficacy analyses, based on baseline disease severity (sPGA score, PASI \leq 20 vs $>$ 20), revealed that greater baseline disease severity generally correlated with greater magnitude of treatment effect. Because of these factors, I find that the results of primary endpoint, based on all enrolled subjects, are acceptable and supported rather than undermined by subgroup analyses of subjects with greater disease severity. The reader is referred to the clinical and statistical reviews by Drs. Epps and Fritsch, respectively, for a full discussion of the trial design and results, including the open label and randomized withdrawal retreatment phases.

I agree with the conclusions reached by Dr. Fritsch, the biostatistics reviewer, and Dr. Trajkovic, the cross-disciplinary team leader (CDTL), that the applicant demonstrated the efficacy of etanercept in the treatment of moderate to severe psoriasis in children 4 to 17 years of age. In addition, I concur with Dr. Trajkovic that efficacy can also be extrapolated from the adult indication, as the pathophysiology of plaque psoriasis is understood to be similar in children and adults, and there are not known age-related factors that would make the disease either more or less

responsive to treatment in pediatric patients. I also acknowledge that Dr. Epps, the clinical reviewer, reached a different conclusion when reviewing the data provided in support of this application; the reader is referred to her clinical review for a full discussion of her rationale and concerns.

8. Safety

The applicant submitted data from Study 20030211, a 48-week trial with an initial 12-week placebo-controlled phase, and Study 20050111, a 264-week open label extension study. In this database, 210 subjects received at least one dose of etanercept; 206 subjects were exposed to study drug for at least 3 months, 199 for at least 6 months, 179 for at least 12 months, 153 for at least 24 months, 125 for at least 36 months, and 103, 79 and 18 for at least 48, 60 and 72 months, respectively. In addition, the applicant submitted postmarketing safety data. The size of the safety database is adequate.

No deaths, malignancies, or opportunistic infections were reported during the pediatric development program (Studies 20030211 and 20050111). Four serious adverse events (SAE) were reported in three subjects during Study 20030211: i) ovarian mass (benign), ii) pneumonia, and iii) dehydration and gastroenteritis. The SAE of pneumonia was considered by the investigator to be related to study drug, and the study drug was discontinued. The SAEs in the other two subjects were not considered to be related to study drug; study drug was discontinued in the subject with the ovarian mass, but was continued in the subject with gastroenteritis and dehydration. Common adverse events include upper respiratory tract infection, headache, influenza and gastroenteritis. Review of adverse event data did not reveal new safety signals.

The applicant reviewed Enbrel post marketing data across all pediatric use as well as specifically for pediatric psoriasis. In the psoriasis pediatric post marketing data, one death was reported due to suicide in a 17 year old male; limited case information precluded causality determination. Enhanced pharmacovigilance of malignancies in patients ≤ 30 years of age at time of malignancy diagnosis, in place since 2011, included one case of lymphoma in an 8 year old female with psoriasis. Hepatosplenic T-cell lymphoma (HSTCL) has been reported in a single adult with psoriasis but no children with psoriasis. Of the postmarket-reported cases of HSTCL associated with etanercept use (all indications), all but one have been confounded by prior or concurrent treatment with azathioprine or mercaptopurine, both of which are genotoxic drugs with warnings for the risk of malignancy and HSTCL. While the relative weakness of the enhanced pharmacovigilance signal for malignancy with etanercept is reassuring, it does not establish absence of risk.

The reader is referred to the clinical review by Dr. Epps and the CDTL review by Dr. Trajkovic for a full discussion of the safety data. Dr. Epps expressed concern about the potential risk for malignancy and serious infections, but acknowledged that these are known risks for etanercept and TNF inhibitors. I concur with Drs. Epps and Trajkovic that no new safety signals were identified for inclusion in labeling.

9. Advisory Committee Meeting

The current supplement was not presented to the Dermatology and Ophthalmology Advisory Committee (DODAC) for review because the prior supplement (5350), which sought approval for the treatment of moderate to severe psoriasis in pediatric patients ages 4 to 17 years, had been presented to DODAC on June 17, 2008. The committee recommended approval at that time. Supplement 5350 contained data from Study 2030211; the current supplement also includes data from Study 20040210, as well as additional postmarketing pharmacovigilance information.

In 2008, supplement 5350 for treatment of moderate to severe psoriasis in children ages 4 to 17 was presented to DODAC. The committee voted in favor of approval of the application at that time. Specific questions with vote tallies (Y=yes, N=no, A=abstain) included:

- a. Do the benefits of etanercept therapy in the treatment of children with moderate to severe plaque psoriasis outweigh the risks?
Y: 7 N: 5 A: 1
- b. Should etanercept be approved for the treatment of moderate to severe plaque psoriasis in children?
Y: 8 N: 5 A: 0
- c. For use in the 4 to 17 year age group?
Y: 7 N: 0 A: 6
- d. Has the applicant provided sufficient information to demonstrate efficacy of etanercept in the pediatric population?
Y: 12 N: 0 A: 1
- e. Has the applicant provided sufficient information regarding the risk of infection in the target pediatric population?
Y: 12 N: 1 A: 0
- f. Has the applicant provided sufficient information regarding the risk of malignancy in the target pediatric population?
Y: 4 N: 7 A: 2
- g. The applicant has agreed to conduct post-marketing safety study 20040210. This long term study is intended to provide safety information regarding the use of etanercept in adult patients. Does the committee recommend approval of etanercept in pediatric patients prior to the completion of this safety study?
Y: 9 N: 3 A: 1

The current supplement contains data from Study 2030211, which also was submitted in supplement 5350, as well as data from Study 20040210 and additional postmarketing pharmacovigilance information. Because DODAC previously recommended approval of supplement 5350, and the additional information in the current supplement did not identify new safety signals, it was not thought necessary to present the application to the committee again.

10. Pediatrics

Consultation was obtained from Office of Pediatric Ethics to inform the Regulatory Briefing (discussed below). Dr. Nelson noted that protection of children requires data to support the safe, effective use of drugs and biologics in pediatric patients, and that absent a clear warning or contraindication, pediatric studies to inform the risks and benefits of a product should be performed, preferably before or soon after adult approval to minimize the risks presented by off-label use without the benefit of adequate data to inform clinical decision-making; such use may also impede conduct of pediatric studies.

The application was presented to the Pediatric Review Committee (PeRC) on August 17, 2016. PeRC agreed with the Division that the safety and efficacy information supported approval for use in the pediatric population.

11. Other Relevant Regulatory Issues

On July 22, 2016, the Division presented the application at a Regulatory Briefing, an internal advisory meeting at which input from OND management was obtained. The panel agreed that the applicant had demonstrated the efficacy and safety of etanercept in the treatment of moderate to severe psoriasis in children 4 to 17 years of age, and supported approval of the supplemental application.

There are no unresolved relevant regulatory issues.

12. Labeling

All components of labeling were reviewed.

The Indication and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, and Clinical Trials sections were revised to include information about treatment of plaque psoriasis in children 4 years of age and older. In coordination with the Division of Pulmonary, Allergy and Rheumatology Products, information about defunct Pregnancy and Lactation Surveillance programs was removed from professional and patient labeling. Other minor changes were made to conform to current labeling standards.

Quality information in all aspects of labeling was revised for consistency and clarity with regard to strength, presentation, dosage form and route of administration.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval
- Risk Benefit Assessment
Psoriasis is a chronic inflammatory disease that primarily affects the skin, has comorbidities in other organs and substantially impairs quality of life. The impact of the disease is particularly severe for children, who suffer the physical and psychological burden of their disease during crucial developmental years. For adult patients with moderate to severe disease, there are numerous approved systemic options that allow for

treatment consistent with clinical guidelines; however for children, there are no approved systemic therapies. Thus, in order to treat the disease and minimize physical and psychological morbidity, healthcare providers, parents and pediatric patients with moderate to severe psoriasis have had to resort to off-label use of drug and biologic products without the benefit of relevant information in product labeling to inform their decisions.

The applicant submitted information from clinical studies and postmarketing pharmacovigilance to demonstrate the efficacy and safety of etanercept in the treatment of moderate to severe psoriasis in children 4 to 17 years of age. Efficacy versus placebo was demonstrated for PASI 75 and sPGA response, as well as PASI 90. No new safety signals were identified. Treatment with etanercept is not without risk, but the risks are recognized, conveyed in labeling, and justified by the potential benefits, especially in the pediatric population for whom morbidity (due to developmental status and potential disease duration) and need (due to absence of approved systemic treatment alternatives) are the greatest.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies: None
- Recommendation for other Postmarketing Requirements and Commitments: None

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/s/

JILL A LINDSTROM
11/04/2016