*FOOD AND DRUG ADMINISTRATION*

CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Pulmonary, Allergy, and Rheumatology Products
10903 New Hampshire Avenue
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# Medical Officer Review

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| **BLA/Supplement:** | 761042/10 |
| **Drug Name:** | Erelzi (etanercept-szzs) |
| **Sponsor:** | Sandoz, Inc |
| **Indication:** | Rheumatoid Arthritis (RA), Ankylosing Spondylitis (AS), Juvenile Idiopathic Arthritis (JIA) |
| **Type of Submission:** | Prior Approval Supplement |
| **Date of Submission:** | December 20, 2018 |
| **Review Date:** | October 17, 2019 |
| **Review Team:** | Rachel L. Glaser, M.D., DPARP, ODEII<br>Nancy Xu, M.D., Associate Director for Labeling, DDDP, ODEIII<br>Gary Chiang, M.D., M.P., DDDP, ODEIII<br>David Kettl, M.D., Clinical Team Leader, DDDP, ODEIII<br>Shari Targum, M.D., Associate Director, DDDP, ODEIII<br>Nikolay P. Nikolov, M.D., DPARP Designated Signatory |
| **Project Manager:** | Brandi Wheeler, R.P.M. |

**Synopsis**: This review outlines the Division's review and general agreement with the proposed indication changes as well as labeling changes to the Erelzi USPI and Medication Guide. These modifications are proposed by the Applicant to update the labeling to include the indications of psoriatic arthritis (PsA) and adult plaque psoriasis (PsO). Erelzi was licensed on August 30, 2016 for the treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis in patients aged 2 years and older, ankylosing spondylitis, PsA, and adult PsO. Accordingly, the PsA and adult PsO indications and certain related information were included in the originally-approved labeling. The Applicant subsequently submitted a supplement seeking

removal of those indications as well as certain related information from the labeling, which was approved on January 26, 2018. In the current submission, the Applicant seeks to update the labeling to include the PsA and adult PsO indications as well as certain related information to the labeling. (b) (4)

Additional revisions are proposed to incorporate relevant information from US-licensed Enbrel labeling approved in October 2018. FDA reviewed the proposed labeling changes to ensure that the labeling meets the standards for approval. FDA's review was informed, in part, by the principles set forth in the Agency's guidance *Labeling for Biosimilar Products* (July 2018). The Agency does not evaluate patents in reviewing proposed biosimilar labeling. The proposed labeling changes are acceptable.

**Review**

**1. Regulatory History**

Erelzi (etanercept-szzs) is a dimeric fusion protein, consisting of an extracellular ligand-binding portion of the human p75 tumor necrosis factor receptor (TNFR) which is linked to the Fc domain of human IgG1. It binds to and neutralizes pro-inflammatory cytokines TNF-α and lymphotoxin-α by preventing binding to natural cell surface receptors and subsequent signal transduction. The BLA for Erelzi was approved on August 30, 2016 as a biosimilar to US-licensed Enbrel for treatment of the following indications: rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis in patients aged 2 years or older, PsA, ankylosing spondylitis (AS), and adult PsO.

The Applicant subsequently submitted a supplement seeking removal of the PsA and adult PsO indications as well as certain related information from the labeling on January 26, 2018. According to the cover letter for that prior approval supplement (S-001) the supplement was "to seek approval for a carve-out label for the initial commercial batch of ERELZI, by omitting previously approved indications, Psoriatic Arthritis (PsA) and Plaque Psoriasis (PsO) from the label, as these indications remain protected by patents until August 13, 2019." In the current prior approval supplement, submitted on December 20, 2018, Sandoz seeks to update the labeling to include the PsA and adult PsO indications as well as to add certain related information to the labeling "upon expiry of the relevant patents on August 13, 2019." Note, the Agency does not evaluate patents in reviewing proposed biosimilar labeling. In response to an information request (response dated February 11, 2019), Sandoz confirms that the current supplement is seeking to update the labeling to include the PsA and adult PsO indications (b) (4)

**2. Proposed Changes to the Indications**

FDA has reviewed the Applicant's submissions and has determined that the information in the BLA, including this supplement, supports the addition of the PsA and adult PsO indications.

[1] FDA-approved Enbrel labeling

This includes the results of the comparative clinical study in patients with moderate to severe PsO and the August 29, 2016 CDTL's determination that the Applicant provided scientific justification (based on the mechanism of action, pharmacokinetics, immunogenicity, and toxicity) to support extrapolation of data and information to support licensure of Erelzi for the PsA indication. Therefore, approval is recommended of this supplement to add the PsA and adult PsO indications. See also DDDP memo dated October 17, 2019.

**3. Proposed Changes to the Prescribing Information**

Revisions proposed in this submission include revisions intended to update the labeling to include the indications of PsA and adult PsO, as well as revisions made to incorporate relevant information, where appropriate, from the US-licensed Enbrel labeling approved in October 2018.

Revisions in the proposed USPI update the labeling to include the indications of PsA and adult PsO to the 'Indications and Usage' and 'Dosage and Administration' sections. Other sections of the label were similarly updated to include references to PsA and adult PsO, and to the data from associated clinical studies.

As stated in the Clinical Review dated January 26, 2018, in the prior supplement (S-001), references to PsA and PsO were replaced with "another indication" when "the data from the indication could not be separated, such as when pooled data was presented, or when the information regarding the indication is to be maintained to convey safety information." Additionally, "[i]n sections of the USPI where data was specific to the indication being removed and does not impact safe use of the product, this information was removed from the labeling."

In the current supplement, references to "other indications" have been revised to PsA and/or adult PsO. Data specific to these indication(s) have been included. An example of this approach is shown below:

Immunogenicity

Patients with RA, PsA, AS or PsO, ~~and two other indications~~ treated with etanercept were tested at multiple time points for antibodies to etanercept. Antibodies to the TNF receptor portion or other protein components of etanercept were detected at least once in sera of approximately 6% of adult patients with RA, PsA, AS or PsO ~~or two other indications~~. These antibodies were all non-neutralizing. Results from JIA patients were similar to those seen in adult RA patients treated with etanercept.

In adult PsO studies that evaluated the exposure of etanercept for up to 120 weeks, the percentage of patients testing positive at the assessed time points of 24, 48, 72 and 96 weeks ranged from 3.6%-8.7% and were all non-neutralizing. The percentage of patients testing positive increased with an increase in the duration of study; however, the clinical significance of this finding is unknown. No apparent correlation of antibody development to clinical response or adverse events was observed. The immunogenicity data of etanercept beyond 120 weeks of exposure are unknown.

In Section 6.2 'Immunogenicity,' proposed revisions were made to change "Patients with RA, AS, and two other indications" to "Patients with RA, PsA, AS or PsO," as well as to include the immunogenicity data specific to the PsO studies in adults.

In keeping with this approach, the following revisions were also made:

Section 5.3 ‘Lymphomas’ and ‘Melanoma and Non-Melanoma Skin Cancer (NMSC)’ was updated from “adult patients with RA, AS and another indication” to “adult patients with RA, AS, and PsA,” The statements of the incidences of lymphoma and NMSC events in adult PsO patients were updated.

In Section 6.1, references to “other indication” and “another indication” were changed to PsA and/or PsO. The description of serious infections in patients in clinical trials in PsO was included.

Similarly, in Section 6.1 ‘Injection Site Reactions,’ data regarding the proportion of PsO patients with injection site reactions was included. The summary statement that observed adverse reactions were similar in patients with RA as patients with AS was updated to also include PsA patients. Presentation of adverse reactions in adult PsO patients in the clinical trials was also included.

> *Reviewer’s comment: The proposed revisions to update the labeling to include the references to PsA and PsO in the Warnings and Precautions and Adverse Reactions sections are acceptable from a clinical perspective.*

In Section 7.1 ‘Vaccines’, data regarding vaccine response in PsA patients was updated.

In Section 8 ‘Use in Specific Populations’ the description of the Organization of Teratology Information Specialists Pregnancy Registry was updated from “in women with rheumatic diseases or another indication” to “in women with rheumatic diseases or psoriasis.” Section 8.5 was revised to include discussion of geriatric patients with PsO.

Section 12 ‘Clinical Pharmacology’ was revised to include specific reference to PsA and PsO in the description of the role of TNF. A statement of the trough concentrations in adult PsO patients was included.

Sections 14.3 and 14.5 describing clinical studies in PsA and adult PsO, respectively, were updated.

Changes proposed to align with the US-licensed Enbrel label include:

In Section 13.1, the statement that no evidence of mutagenic activity was observed in *in vitro* and *in vivo* studies is deleted.

In addition to the changes proposed by the Applicant, additional modifications were made to align with the recommendations of the FDA Guidance: Labeling for Biosimilar Products and for consistency with US-licensed Enbrel.

> *Reviewer’s comment: The proposed revisions to update the labeling to include the PsA and adult PsO indications, are acceptable with the modifications discussed above. Revisions made to align with the US-licensed Enbrel are acceptable.*

**4. Proposed Changes to the Medication Guide**

Proposed revisions to the Medication Guide (MG) update the labeling to include PsA and PsO in adults to the list of conditions Erelzi is used to treat. Additional modifications were made by the Agency for consistency with the US-licensed Enbrel. There are no proposed changes to the Instructions for Use.

> *Reviewer’s comment: The proposed revisions to the MG are acceptable.*

## 5. Pediatrics

The Agency has determined that the proposed update to the labeling to include the PsA and adult PsO indications triggers Pediatric Research Equity Act (PREA). The supplement's pediatric plan was discussed at the PeRC meeting on October 08, 2019. The PeRC agreed with the plan to issue a postmarketing required assessment of Erelzi for the treatment of plaque psoriasis in patients 4 years to 17 years of age. Respectively, this supplement will be approved with the following PREA postmarketing required assessment:

> Assessment of Erelzi (etanercept-szzs) for the treatment of plaque psoriasis in patients 4 years to 17 years of age.
>
> Final Report Submission: January 2020

Refer also to memo dated October 17, 2019.

## 6. Summary of Changes and Recommendations

The Applicant seeks to update the labeling to include the PsA and adult PsO indications as well as certain related information to the USPI and MG. Additional revisions are proposed to incorporate relevant information from the US-licensed Enbrel labeling. Thus, we recommend approval of this supplement. The proposed indication and labeling updates were also reviewed by the collaborating review team from the Division of Dermatology and Dental Products (DDDP). The DDDP labeling reviewer agreed with the addition of the adult PsO indication and labeling changes pertinent to the adult PsO indication. DDDP clinical review team also agrees with the plan to issue a post-marketing required assessment for pediatric PsO.

## Regulatory Action

The regulatory action is Approval of Supplement 010.

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/s/

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10/17/2019 03:34:19 PM

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10/17/2019 04:03:18 PM
Signed under the authority delegated by Dr. Sally Seymour, Division Director, DPARP.