BLA 761180-S001 ADBRY (tralokinumab) solution for injection, Cycle #2 resubmission on 6/16/2023.

1 Executive Summary

1.1. Product Introduction

ADBRY (tralokinumab) is an IgG4 Anti-IL-13-Rα1/α2 monoclonal antibody licensed by the FDA on 12/27/2021 for the indication of treatment (with or without topical corticosteroids) of moderate to severe Atopic Dermatitis (AD) in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

The Applicant (LEO Pharma A/S) submitted a Prior Approval Efficacy Supplement (S-001) on 1/14/2022 under the regulatory pathway 351(a) of the Public Health Service Act to broaden the patient population from "adult patients" to "patients aged 12 years and older" (with moderate to severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable) in labeling upon approval of this supplement. ADBRY can be used with or without topical corticosteroids.

Additionally, the clinical trial LP0162-1334 (ECZTRA 6) report, is also intended to fulfill the Pediatric Research Equity Act (PREA) Postmarketing Requirement (PMR) 4015- 1 issued at the time of initial BLA licensure.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Agency's first cycle review of BLA 761180-S001 on 2/10/2022 received a Complete Response (CR) due to insufficient time for the Agency to review the supporting information regarding the user interface and human factors information for the 150 mg Q2W dose submitted by the Applicant late in the review cycle .

The first cycle review of the efficacy supplement S-001 was based on the analysis of the results from trial LP0162-1334 (ECZTRA 6), conducted in adolescent (12 years ≤ age ≤17 years) subjects with moderate to severe atopic dermatitis (defined as baseline affected BSA≥ 10%, EASI score ≥16, IGA = 3 (moderate) or 4 (severe), WI-NRS (weekly average)≥ 4, and Body weight ≥ 30 kg) with history of topical corticosteroid (TCS) or topical calcineurin inhibitor (TCI) treatment failure or subjects for whom these topical AD treatments are medically inadvisable. This trial had a 16-week placebo-controlled period, a 36- week maintenance/open-label treatment period, and a 14-week safety follow-up period.

The primary efficacy endpoint for this trial was the proportion of subjects achieving an IGA response (IGA score of 0 (clear) or 1 (almost clear) [which included a ≥2-grade reduction from Baseline]). A key secondary efficacy endpoint was EASI75 at Week 16, and a secondary efficacy endpoint (pre-specified and controlled for multiplicity, for which the Applicant seeks labeling claims) was the proportion of subjects WI-NRS response (weekly average) of ≥4-point improvement from baseline at Week 16.

Substantial evidence of efficacy (SEE) was demonstrated based on the analysis of the results from the primary efficacy endpoint. Analysis of the results from the secondary efficacy endpoints were supportive of efficacy.

Analysis of the primary safety database for trial ECZTRA 6 did not identify any new safety signals, was qualitatively similar to the analysis of safety data from clinical trials for tralokinumab conducted for adult subjects and was adequate to characterize the safety profile of tralokinumab for the treatment of moderate to severe AD in adolescent subjects.

The Agency provided the following rationale for a CR action during the Cycle #1 review:
"Due to the dosing administration recommendations for the adolescent population, additional information was requested from the Applicant. The requested Human Factor study results were submitted January 5, 2023, and will need to be reviewed in a second cycle. These data will provide supporting information regarding the user interface and human factors information for the 150 mg Q2W dose, showing that 150 mg Q2W dosing can be used safely in the adolescent population. Due to the timing of this submission so close to the goal date, a Complete Response will be recommended for this supplement and the submitted Human Factors information will need to be considered in a subsequent cycle to allow approval of tralokinumab in the adolescent population. The determination that 150 mg Q2W dosing can be used safely in the adolescent population cannot be made prior to the goal date and a Complete Response is recommended".

A Type A meeting was held with the Applicant on 4/23/2023 to discuss the CR action, and a Cycle#2 resubmission of this sBLA was submitted under SDN 330 on 6/16/2023.
The review team reviewed the following data during review cycle#2 for this sBLA.

1. No new clinical efficacy data was included in the resubmission package for BLA 761180-S001. Following the review of the efficacy data for trial ECZTRA 6 (included under the initial submission of BLA 761180-S001) during review cycle#1, the review team had concluded that substantial evidence of efficacy (SEE) had been demonstrated for adolescent subjects with moderate to severe AD treated with tralokinumab.
2. A safety update report (ISS safety update- adolescents in M 5.3.5.3) for adolescent subjects in the tralokinumab ongoing trials (ECZTEND and INJECZTRA) and the Ex-US postmarketing safety data for adolescent subjects with a cut-off date of 12/16/2022 was submitted with the resubmission package for this sBLA. This safety update report was consistent with the safety profile of tralokinumab for adolescent subjects reported under Cycle # 1 review for this supplement and did not identify any new safety concerns.
3. A labeling consult review (in DARRTS on 11/13/2023) by David Foss, Regulatory Review Officer, Office of Prescription Drug Promotion (OPDP) of the PI did not provide any comments to convey to the Applicant.
4. A Patient Labeling Review (in DARRTS on 11/16/2023) of PPI and IFU by Ruth Mayrosh, PharmD, Senior Patient Labeling Reviewer, Division of Medical Policy Programs (DMPP) and David Foss, PharmD, MPH, BCPS, RAC Regulatory Review Officer Office of

Prescription Drug Promotion (OPDP) concluded that "the PPI and IFU is acceptable with our recommended changes" to convey to the Applicant.

5. A Human Factors Study Report and Labels and Labeling Review (in DARRTS on 11/16/2023) by Matthew Barlow, RN, BSN, DMEPA 1 Human Factors Evaluator included the following conclusion and recommendations to convey to the Applicant:

   " The results of the HF validation study demonstrate that representative users can use the product safely and effectively. However, our review of the HF validation study results identified additional mitigations that can be implemented to address the use issues….
   We found the results of your human factors (HF) validation study acceptable. However, our review of the HF validation study results identified additional mitigations that can be implemented to address some use issues. We have provided recommendations below, and we recommend that you implement these recommendations prior to approval of this BLA Supplement:

   A. Instructions for Use

      a. Based on the results and subjective feedback for the knowledge task of "Pinch the skin as needle is inserted", we recommend revising figures J, K, and L to have the text "pinch" with an arrow pointing to the fold of skin in each figure to further emphasize this important administration technique.

      b. Based on the results and subjective feedback for several knowledge tasks related to storage, we recommend revising these sections to improve prominence and emphasize the important information within these sections. For example, you could consider headings with color and/or other grouping principles to make the "Storing Adbry" section more prominent.

      c. Based on the results and subjective feedback for the knowledge task of "check seal on carton", we recommend revising statement found under step 1b to improve prominence of this important information. Consider moving the statement "Do not use the Adbry prefilled syringes if the seal on the carton is broken" to a separate bullet point".

6. A label and labeling review by Madhuri R. Patel, PharmD, DMEPA 1 Acting Team Leader (in DARRTS on 11/20/2023) included the following: "Our evaluation of the proposed Adbry Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), container labels, and carton labeling did not identify areas of vulnerability that may lead to medication errors. We have no recommendations at this time".

7. A memorandum of Assessment by the CDER/OPQ/OBP/DBRR II Primary Assessor, Meng "Chloe" Rowland, Ph.D., (in Panorama on 11/3/2023) concluded that this efficacy supplement was acceptable from an OBP product quality perspective, and recommended approval of this supplement from the product quality perspective.

This reviewer concurs with the assessment from the review team that all of the issues in the Complete Response action letter have been adequately addressed and the application can be approved pending agreement with the applicant of final labeling.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HAMID N TABATABAI
12/14/2023 02:50:59 PM

DAVID L KETTL
12/14/2023 03:02:40 PM