Clinical Review and Evaluation/Division/Summary Memorandum
Resubmission of BLA 761306

Supporting Document Number: 61

Sponsor: Eli Lilly and Company

Drug: EBGLYSS (lebrikizumab-lbkz)

Proposed Indication: Treatment of adult and pediatric patients 12 years of age and older who weigh at least 40kg with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Correspondence Date: March 14, 2024

Review Date: September 13, 2024

Primary Reviewer: Roselyn E. Epps, M.D., FAAP, FAAD
Division of Dermatology and Dentistry (DDD), Office of Immunology and Inflammation (OII), Office of New Drugs (OND)

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Background

This memorandum summarizes the review of the information in the resubmission of BLA 761306 in response to the Agency's Complete Response (CR) letter dated September 28, 2023, for EBGLYSS (lebrikizumab) for the treatment of moderate-to-severe atopic dermatitis in patients 12 years of age and older who weigh at least 40kg with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

The CR letter listed several deficiencies that were all related to drug substance and drug product manufacturing facilities. The Applicant resubmitted BLA 761306 on March 14, 2024. This resubmission is considered a complete response to deficiencies stated in the CR letter on September 28, 2023. In the response, the Applicant additionally submitted study J2T-MC-KGAK/DRM06-AD18, entitled: A Phase 3, 16-week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Impact of Lebrikizumab on Vaccine Responses in Adult Patients with Moderate-to-Severe Atopic Dermatitis.

Efficacy and Safety

The efficacy and safety of EBGLYSS were established following the review of clinical data during the first review cycle.

The Applicant provided substantial evidence of effectiveness from two adequate and well-controlled trials (Studies KGAB and KGAC) and one supportive trial (Study KGAD) that evaluated EBGLYSS for treatment of adult and adolescent subjects 12 years of age and older with moderate-to-severe atopic dermatitis whose disease was not adequately controlled with topical prescription therapies or when those therapies were not advisable. Studies KGAB and KGAC evaluated lebrikizumab as a monotherapy, and the supportive Study KGAD evaluated lebrikizumab with protocol-specified, concomitant use of topical corticosteroids (TCS). For Studies KGAB and KGAC in the target AD population, lebrikizumab was statistically superior to placebo for the primary endpoint of IGA success (defined as scoring 0 or 1 with ≥ 2-point reduction from Baseline) and key secondary endpoints EASI-75 (≥75% reduction from Baseline), at Week 16. The proportions of IGA responders in the 250 mg Q2W regimen recommended for approval were 43.1% and 33.2% in the monotherapy trials, compared with 12.7% and 10.8% in the respective placebo groups. The proportion of EASI-75 responders in the 250 mg Q2W regimen recommended for approval were 58.8% and 52.1% in the monotherapy trials, compared with 16.2% and 18.1% in the respective placebo groups. Regarding the key secondary endpoints, lebrikizumab was statistically superior to placebo for EASI-90 and pruritus NRS score (i.e., at least a 4-point reduction from Baseline in Worst Daily Pruritus NRS score), at Week 16 in the monotherapy trials.

The Applicant adequately characterized the safety profile of EBGLYSS through analyses of data from the safety database of 1756 subjects, including 382 adolescents. The safety profiles were similar whether lebrikizumab was administered as monotherapy or with concomitant topical corticosteroids. The most frequently reported adverse reactions were conjunctivitis, injection site reactions, and herpes zoster infections. No deaths were reported among subjects receiving lebrikizumab during the placebo-controlled induction period. Four deaths were reported among subjects receiving lebrikizumab (1 during the maintenance escape period, 2 during the long-term extension study, and 1 during the open-label Study KGAE), though none was considered likely related to study drug.

Additionally, in the resubmission, the Applicant submitted the results from an unsolicited study with the stated objective to assess the vaccine response in adults with atopic dermatitis, referred to as study KGAK, entitled: A Phase 3, 16-week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Impact of Lebrikizumab on Vaccine Responses in Adult Patients with Moderate-to-Severe Atopic Dermatitis. A brief summary follows:

<u>Study KGAK Design</u>
The study randomized and treated 254 subjects.
The Main Criteria for Inclusion:

- Adult, male or female, aged 18 to 55 years
- A diagnosis of chronic AD, as defined by the American Academy of Dermatology Consensus Criteria, for at least 1 year before the screening visit
- Moderate-to-severe AD, defined as having all the following at the Baseline visit
    - Eczema Area and Severity Index (EASI) of 16 or more
    - Investigator's Global Assessment (IGA) score of 3 or more, and
    - body surface area of 10% or more

- A history of inadequate response to treatment with topical medications or determination that topical treatments are otherwise medically inadvisable
- Not received any tetanus-containing vaccine within approximately 5 years of randomization, and
- Never received a meningococcal conjugate vaccine or have received not more than 1 prior MCV dose at least 4 years prior to randomization, of a vaccine containing 1 or more meningococcal serogroups (serogroups A, C, W, Y).

The co-primary endpoints were:

- Percentage of subjects who developed a booster response to tetanus toxoid 4 weeks after the administration of the Tdap vaccine at Week 16, and
- Percentage of subjects who had a positive antibody response to Meningococcus C antigen of the MCV 4 weeks after the administration of the vaccine at Week 16.

Subjects were randomized 1:1 to either lebrikizumab or placebo arms during the Blinded Treatment Period. All study drugs were administered by sterile, preassembled pre-filled syringe.

- Lebrikizumab: 2 mL 250 mg Q2W: a loading dose of 500 mg lebrikizumab administered at Baseline and Week 2, and 250 mg Q2W thereafter through Week 14. This is the same dosing and treatment regimen used in then-ongoing Phase 3 lebrikizumab studies.
- Placebo: 4 mL administered at Baseline, and Week 2 and 2 mL Q2W thereafter through Week 14

At Week 12, baseline pre-vaccine titers were obtained. The following vaccines, one dose, were administered to all subjects on study drug:

- Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (Sanofi) (Tdap), and
- Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine (GlaxoSmithKline) (MCV).

Assessment for a positive antibody response to Tdap and MCV was obtained at Week 16.

The analyses were conducted on a modified intent-to-treat population (mITT). A directed audit resulted in data exclusion from two sites due to non-compliance with protocol entry criteria related to AD severity at baseline and lack of source documentation for eligibility of the participants. The Applicant considered data from the two sites unreliable, inconsistent, and/or missing source documentation.

Study KGAK Results:

The mITT population (247) consisted of 125 lebrikizumab and 122 placebo subjects. More subjects completed the study in the lebrikizumab arm (113, 90.4%) compared to the placebo arm (89, 73%). The demographic characteristics were comparable across lebrikizumab and placebo arms.

The co-primary endpoint of the percentage of participants who developed a booster response to tetanus toxoid 4 weeks after the administration of the Tdap vaccine at Week 16 (73.6%) compared to placebo (73.4%) was met. The co-primary endpoint of the percentage of participants who had positive antibody response to Meningococcus C antigen of the MCV 4 weeks after the administration of the vaccine at Week 16 (86.9%) compared to placebo (75.0%) was met.

The modified safety population numbered 247 subjects. Few subjects in the lebrikizumab arm (4.1%) and the placebo arm (2.4%) discontinued due to adverse events (AEs). Treatment-emergent adverse events (TEAEs) were reported for a higher proportion in the lebrikizumab group (8.8%) compared to the placebo group (4.1%). The most common TEAEs included COVID-19 infection, nasopharyngitis, headache, atopic dermatitis, and conjunctivitis. The two serious adverse events reported, breast cancer stage II (lebrikizumab arm) and atopic dermatitis (placebo arm), were considered unrelated to study drug; rates of SAEs were 0.8% for both groups. No deaths were reported.

Labeling recommendations for the vaccine response study

BLA 761306 resubmission includes data from study KGAK, described above. Assessment of comparative humoral immune responses provides a limited assessment of the effects of lebrikizumab on immune responses to vaccination, does not inform the durability of immune response, and these endpoints are not established correlates of protection. As a result, the study results do not assess clinical effectiveness of vaccination in patients treated with lebrikizumab and inclusion of the proposed changes to the prescribing information is not supported.

The review team recognizes the precedent of including language from similar studies in other immunomodulatory products in the past. However, the Agency's thinking regarding inclusion of vaccine response study results in labeling for immunomodulatory therapies has evolved in response to the changing scientific landscape. Vaccine response studies were initially required for some of the immunosuppressive products. The purpose of these studies was to assess the impact of a new immunomodulatory therapy on B and T cell responses to vaccination(s) that patients may need as part of their clinical care. However, recognizing that the immune response measured after vaccination may not be a clinical correlate for protection, the Agency has reconsidered the importance of including information from such studies in product labeling.

Given these limitations and challenges, the Agency no longer requires these studies for many immunomodulatory programs.

Office of Pharmaceutical Quality - Deficiencies

Following the review of submitted data and re-inspection of manufacturing facilities, the Office of Pharmaceutical Quality team has recommended approval in their August 27, 2024, review.

Labeling

The Applicant submitted labeling with the March 14, 2024, CR resubmission, and container label and carton labeling on July 29, 2024. The Division consulted the Division of Medication Error Prevention and Analysis 1 (DMEPA 1) and Division of Medical Policy Programs (DMPP), which reviewed the submission; the Agency recommendations were incorporated by the Applicant. The finalized Prescribing Information, patient labeling, instructions for use, and carton and container labeling were agreed upon with the Applicant and will be included with the Approval letter.

Postmarketing Requirements

Though no safety signals have been observed with the use of lebrikizumab during pregnancy, the information is limited to inform of maternal adverse reactions or drug-associated risk of developmental outcomes. The following pregnancy-related postmarketing requirements (PMR) were issued.

1. PMR:
   Conduct or participate in a relevant Pregnancy Exposure Registry, a prospective registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to lebrikizumab during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, neonatal deaths, and serious infections, will be assessed through at least the first year of life. (Plan to Submit Draft Protocol: March 2025)

2. PMR:
   Conduct an additional pregnancy study that uses a different design from the Pregnancy Exposure Registry (for example a retrospective cohort study using claims or electronic medical record data with outcome validation or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to lebrikizumab during pregnancy compared to an unexposed control population. (Plan to Submit Draft Protocol: March 2025)

During the first review cycle, BLA submission of a new molecular entity triggered PREA Postmarketing requirements. The Applicant submitted two protocols for studies to assess the long-term safety of lebrikizumab in pediatric subjects 6 months to < 18 years of age with moderate to severe atopic dermatitis. The studies are ongoing at the time of approval

3. PMR:
   Conduct a randomized, double-blind, placebo-controlled trial to assess the PK and safety of lebrikizumab in pediatric patients 6 months to <6 years, 6 years to <12 years, and ≥12 years to <18 years weighing <40 kg with moderate to severe atopic dermatitis.

   (b) (4)

4. PMR:
   Conduct an open-label, long-term extension study to evaluate the long-term safety of lebrikizumab in pediatric patients 6 months to <12 years, and ≥12 years to <18 years weighing <40 kg with moderate to severe atopic dermatitis.

Summary and Recommendation:

The benefit/risk profile of EBGLYSS (lebrikizumab) is unchanged since the previous review cycle and all CMC deficiencies have been addressed by the Applicant. Therefore, this reviewer recommends approval and licensing of lebrikizumab (EBGLYSS) for the treatment of adult and adolescent patients 12 years of age and older who weigh at least 40 kg with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Division Leadership Conclusion

I concur with the review team recommendations to approve EBGLYSS (lebrikizumab) for the treatment of adult and adolescent patients 12 years of age and older who weigh at least 40 kg with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Deficiencies identified in a Complete Response letter from September 28, 2023, were adequately addresses with this resubmission, and the safety and effectiveness of lebrikizumab in the treatment of atopic dermatitis were established during original review cycle.

In addition, the statistical review team conducted sensitivity analyses for the pruritus NRS endpoints comparing the revised approach, which required at least 4 out of 7 days for baseline and 1 out of 7 days for post-baseline periods, with the originally defined SAP approach, which required at least 4 out of 7 days for baseline and post-baseline periods. For the original SAP approach, participants who did not have at least 4 out of 7 days at a post-baseline visit were treated as having missing data and imputed using MCMC-MI.

The findings indicate that the sensitivity analyses align with the primary analyses with the revised approach, demonstrating no observed impact on the conclusions and very minimal impact on the point estimates.

Additional safety data will be collected under 4 PMRs (2 for EBGLYSS-exposed pregnancies and 2 for pediatric sub-populations as described above).

The labeling discussions with the Applicant are concluded, and the labeling is deemed adequate to ensure the safe use of EBGLYSS.

Office Signatory Conclusion

Eli Lilly and Company (Applicant) resubmitted this biologics licensing application (BLA) for lebrikizumab-lbkz (tradename EBGLYSS), seeking approval of this interleukin-13 antagonist for the treatment of moderate to severe atopic dermatitis.

The resubmission is in response to a Complete Response letter dated September 28, 2023, citing deficiencies in drug substance and drug product manufacturing facilities. Based on the data in the resubmission, and re-inspection of the manufacturing facilities, the Office of Pharmaceutical Quality team now recommends approval (see review dated August 27, 2024).

The efficacy and safety of EBGLYSS was established following the review of clinical data during the first review cycle, and the reader is referred to the Agency's review from that submission. Briefly, substantial evidence of effectiveness was established based on the results from two adequate and well-controlled trials (KGAB and KGAC) that demonstrated statistically significant and clinically meaningful improvements in the proportion of patients with clear or almost clear skin and reductions in the severity of pruritis. The Applicant adequately characterized the safety profile of lebrikizumab through analyses of data from the safety database of 1756 subjects, including 382 adolescents, across 8 clinical studies. The safety profiles were similar whether lebrikizumab was administered as monotherapy or whether with concomitant topical corticosteroids. The most frequently reported adverse reactions were conjunctivitis, injection site reactions, and herpes zoster infections.

In this resubmission, the Applicant elected to include the results from a vaccine response study, Study KGAK. With regard to safety from that study, Dr. Epps' review identified no clinically important differences in the safety profile. After review and discussion, the team concluded, and this signatory concurs that inclusion in labeling is not necessary to inform safe use of the drug (see rationale above).

The BLA included appropriate preapproval nonclinical and clinical pharmacology studies. Four post-marketing studies will be required to inform safety for pregnant and pediatric patients.

The review team concludes that the improvement in skin clearance and pruritis severity observed with lebrikizumab treatment compared to placebo outweighs the risks when lebrikizumab is used as recommended in the approved labeling. There are no outstanding issues from any review discipline. I concur with the content of the various discipline assessments and their recommendation for approval of lebrikizumab for the treatment of adult and adolescent patients 12 years of age and older who weigh at least 40 kg with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

The regulatory action is Approval of lebrikizumab-lbkz with the agreed upon labeling and post-marketing required studies, detailed above. No risk evaluation and mitigation strategy are warranted.

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/

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