BLA 761306

CORRECTED BLA APPROVAL

Eli Lilly and Company
Attention: Thecla W. Wong
Senior Director, Global Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Thecla W. Wong:

Please refer to your biologics license application (BLA) dated and received September 28, 2022, and your amendments, submitted under section 351(a) of the Public Health Service Act for Ebglyss (lebrikizumab-lbkz) injection.

We acknowledge receipt of your resubmission dated March 14, 2024, which constituted a complete response to our September 28, 2023, action letter.

We also refer to our approval letter dated September 13, 2024, which contained the following error: Incorrect study completion date and final report submission for the PREA PMRs.

This corrected action letter incorporates the correction of the error. The effective action date will remain September 13, 2024, the date of the original letter.

LICENSING

We have approved your BLA for Ebglyss (lebrikizumab-lbkz) injection effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Ebglyss under your existing Department of Health and Human Services U.S. License No. 1891. Ebglyss is indicated for treatment of moderate to severe atopic dermatitis.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture lebrikizumab-lbkz drug substance at (b) (4). The final formulated drug product for the prefilled syringe with needle shield will be manufactured, filled, assembled, and labeled at (b) (4) The final formulated drug product for the prefilled pen will be manufactured, filled, assembled, and labeled at Eli Lilly and Company, Lilly Corporate Center Indianapolis, Indiana 46285 USA. You may label your product with the proprietary name, Ebglyss, and market it as a 250 mg/2 ml injection in a single-dose

prefilled syringe with needle shield, and as a 250 mg/2 mL injection in a single-dose prefilled pen.

DATING PERIOD

The dating period for Ebglyss shall be 36 months from the date of manufacture when stored at 2°C to 8°C, protected from light, in the prefilled syringe with needle shield and 24 months from the date of manufacture when stored at 2°C to 8°C, protected from light, in the prefilled pen. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4)

We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance stored (b) (4) and drug product prefilled pen under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Ebglyss to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Ebglyss, or in the manufacturing facilities, will require the submission of information to your BLA for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert, Instructions for Use). Information on submitting SPL files using eLIST

[1] See http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As (October 2009)*.[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761306**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Ebglyss was not referred to an FDA advisory committee because there were no issues that warranted an advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

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 administration 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, deferred, or inapplicable.

We are waiving the pediatric study requirement from birth to < 6 months of age because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group **and** is not likely to be used in a substantial number of pediatric patients in this group since it may be challenging to establish failure of adequate disease control by topical therapies in children < 6 months of age.

We are deferring submission of your pediatric studies for ages 6 months to < 12 years of age and for pediatric subjects ≥ 12 years to < 18 years of age weighing less than 40 kg for this application because pediatric studies should be delayed until additional safety or effectiveness data have been collected.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 601.28 and section 505B(a)(4)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

4514-1 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.

Final Protocol Submission: 04/2022 (Completed)
Study Completion: 01/2026
Final Report Submission: 04/2026

4514-2 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 <18 years weighing less than 40 kg with moderate to severe atopic dermatitis.

Final Protocol Submission: 01/2023 (Completed)
Study Completion: 01/2028
Final Report Submission: 04/2028

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 119866, with a cross-reference letter to this BLA. Reports of these required pediatric postmarketing studies must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the unexpected serious risks of 1) major and minor congenital malformations, spontaneous abortions, still births, elective terminations, small getational age, preterm birth, and other adverse pregnancy outcomes or an imbalance in the rates of these serious risks in pregnant patients exposed to lebrikizumab compared to an unexposed control population; and 2) effects on postnatal growth and development, neonatal deaths, and serious infections in infants exposed to lebrikizumab in utero.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

4514-3 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.

The timetable you submitted on September 6, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2025
Final Protocol Submission:	09/2025
Study Completion:	09/2035
Final Report Submission:	09/2036

4514-4 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.

The timetable you submitted on September 6, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2025
Final Protocol Submission:	09/2025
Study Completion:	09/2032
Final Report Submission:	09/2033

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Submit clinical protocol(s) to your IND 119866 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

21 CFR 601.70 . We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[5]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements at 21 CFR 600.80.

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements at 21 CFR 600.81.

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.

POST APPROVAL FEEDBACK MEETING

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, contact Tina Wang, Regulatory Project Manager, at 240-402-1773 or Tina.Wang@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Kathleen Donohue, MD
Deputy Office Director
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
  - Instructions for Use
- Carton and Container 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/

NIKOLAY P NIKOLOV
09/13/2024 03:35:55 PM
Signed on behalf of Dr. Kathleen Donohue, Deputy Office Director, OII.