CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761306Orig1s000

OTHER ACTION LETTERS

BLA 761306

COMPLETE RESPONSE

Eli Lilly and Company
Attention: Ana M. Vaz.
Associate VP, GRA-NA
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ana Vaz:

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 lebrikizumab injection.

We have completed our review of this application and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

(1) As part of the facility evaluation of (b) (4) drug substance manufacturing facility, a Remote Regulatory Assessment (RRA) was performed. FDA identified issues during the RRA and conducted a pre-license inspection (PLI) to further evaluate the facility. Following the PLI, FDA conveyed deficiencies to the representative of the facility. FDA has reviewed the responses from the facility, and all deficiencies have not been satisfactorily resolved. Satisfactory responses to these deficiencies should be provided to the inspection team prior to submitting your complete response. Your complete response should include the date of the facility's response to the FDA Form 483. The assessment of the application approvability and resolution of inspection deficiencies would be evaluated upon receipt of the complete response and may include a re-inspection of the facility. Please work with the facility in resolving the related deficiencies.

(2) Following evaluation of the inspection findings noted above, and the response to those findings, the Agency has identified concerns regarding the reliability of data generated at (b) (4) in your BLA submission. The concerns impact data that supports comparability between commercial and clinical materials to ensure expected clinical outcome demonstrated by clinical material can be achieved by commercial material. Further, the adequacy of the proposed lebrikizumab drug substance (DS) manufacturing process and overall control

strategy cannot be determined at this time to support the licensure of lebrikizumab. For resolution, we recommend you engage with an independent third party to develop a protocol for, and conduct, a comprehensive assessment on the impacted information and data submitted in your application to justify the acceptability of using these data and information to support licensure. We recommend you also confirm with the FDA that the protocol is adequate to ensure that the audit will cover the data reliability concerns identified. If any impacted data are removed from the application and/or changes are made to the control strategy to address the facility deficiencies, provide additional information and data (e.g., testing results from repeated studies) that are reliable and accurate to support that consistent process performance and product quality is achieved.

PRESCRIBING INFORMATION

(3) We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

CARTON AND CONTAINER LABELING

(4) We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

(5) Please refer to correspondence dated, December 14, 2022, which addresses the proposed proprietary name, Ebglyss. This name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

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[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
- Present tabulations of the new safety data combined with the original application data.
- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each subject who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

Product Quality:

- Reference is made to your September 13, 2023, response to Question 2 of the FDA September 7, 2023, information request (IR) with respect to the pre-filled syringe needle safety device (PFS-NSD) drug product (DP) manufacturing process at (b) (4). While a re-evaluation of the process validation data against the

new [redacted] (b) (4)) was performed (response to Question 2b), this assessment alone is not sufficient to fully support that the [redacted] (b) (4) process controlled using the revised [redacted] (b) (4) limits is validated for commercial manufacture. Provide additional process validation data, using a scientifically justified number of PFS-NSD process run(s) controlled using the revised [redacted] (b) (4) limits, to fully support the validation of DP [redacted] (b) (4) process.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Qianyiren Song, Regulatory Project Manager, at 301-796-2581.

Sincerely,

{See appended electronic signature page}

Nikolay P. Nikolov, MD
Acting Director
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

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/

KATHLEEN M DONOHUE
09/28/2023 06:32:33 PM
Signing on behalf of Dr. Nikolov.