CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761215Orig2s000

OTHER ACTION LETTERS

BLA 761215/Original 2

COMPLETE RESPONSE

Eli Lilly and Company
Attention: Ingrid Hensley, PhD
Advisor, Global Regulatory Affairs- North America, Diabetes
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Dr. Hensley,

Please refer to your biologics license application (BLA) dated December 17, 2020, received December 18, 2020, and your amendments, submitted under section 351(k) of the Public Health Service Act for Rezvoglar (insulin glargine-aglr) injection, 3 mL (100 Units/mL).

BLA 761215 seeks licensure of Rezvoglar (insulin glargine-aglr) as an interchangeable biosimilar with U.S.-licensed Lantus. For administrative purposes, we have designated the following:

- BLA 761215/Original 1 – biosimilarity
- BLA 761215/Original 2 – interchangeability

The subject of this action letter is BLA 761215/Original2. A separate action letter was issued for BLA 761215/Original 1.

All future submissions to BLA 761215/Original 2 should specify the BLA number and the Original number to which each submission pertains.

We have completed our review of BLA 761215/Original 2, as amended, 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.

REGULATORY

Your application submitted under section 351(k) relies on the same reference product for which a prior biological product received a determination of interchangeability on July 28, 2021. Your application is therefore for a second or subsequent biological product as described in section 351(k)(6) of the Public Health Service Act. Pursuant to section 351(k)(6), FDA shall not make a determination under section 351(k)(4) of the Public Health Service Act that a second or subsequent biological product is interchangeable for any condition of use until the

period of exclusivity described in section 351(k)(6)(A)-(C) has expired. A determination of interchangeability under 351(k)(4) cannot be made for your 351(k) application at this time. The Purple Book contains information on FDA-licensed biological products, including the date of expiration of first interchangeable exclusivity under section 351(k)(6) of the PHS Act if FDA has determined that a biological product is eligible for such exclusivity.

LABELING

We reserve comment on the proposed labeling at this time. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources and Pregnancy and Lactation Labeling Final Rule 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. In addition, we encourage you to review the FDA guidance for industry *Labeling for Biosimilar Products* and FDA draft guidance for industry *Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act*.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at FDA.gov.

CARTON AND CONTAINER LABELING

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

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies of the product under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile and their relevance, if any, to whether there may be clinically meaningful differences between the proposed biosimilar product and the U.S.-licensed reference product.

(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 clinical studies for the proposed indication using the same format as the original BLA submission.

- Present tabulations of the new safety data combined with the original BLA data.

- Include tables that compare frequencies of adverse events in the original BLA with the retabulated frequencies described in the bullet above.

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

(4) Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study 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 BLA data.

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

(7) Provide a summary of worldwide experience on the safety of this product, including adverse events known to be associated with the use of the product and immunogenicity. Include an updated estimate of use for this product marketed in other countries.

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

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. 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 BLA 761215/Original 2 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 Biosimilar Biological Product Sponsors or Applicants.

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

BsUFA II APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for Original 351(k) BLAs under BsUFA II ('the Program'). The BsUFA II Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a BsUFA II applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Shiva Salartash, Regulatory Project Manager, at 301-837-7568.

Sincerely,

{See appended electronic signature page}

Patrick Archdeacon, M.D.
Associate Director for Therapeutics
Division of Diabetes, Lipid Disorders, and Obesity
Office of Cardiology, Hematology, Endocrinology, and Nephrology
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/

PATRICK ARCHDEACON
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