CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761215Orig2s000

SUMMARY REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Division Summary Memorandum for Regulatory Action and Clinical/Cross-Discipline Team Leader Review

Application number:	BLA 761215/Original 2
Product:	Rezvoglar (insulin glargine-aglr)
Indication:	To improve glycemic control in adult and pediatric patients with diabetes mellitus
Applicant:	Eli Lilly and Company
Clinical Review Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Associate Director for Therapeutics and Clinical Team Lead:	Michelle Carey, M.D., M.P.H.
Clinical Reviewer:	Ann Miller, M.D.

The purpose of this memorandum is to provide the Agency's rationale for the determination that Rezvoglar (insulin glargine-aglr) is interchangeable with U.S.-licensed Lantus (insulin glargine).

Background:

Eli Lilly (hereafter referred to as "the Applicant") submitted a biologics license application (BLA) for LY2963016 under section 351(k) of the Public Health Service Act (PHS Act) as a proposed interchangeable biosimilar to U.S.-Lantus (insulin glargine) on December 17, 2020. The Agency received the BLA on December 18, 2020.

The application included, among other things, comparative analytical data, pharmacokinetic/pharmacodynamic (PK/PD) data from a euglycemic clamp study, and a justification for why a comparative immunogenicity assessment was unnecessary to reach an interchangeability determination. The totality of the evidence submitted in the application, including the data and information submitted by the Applicant, demonstrated that LY2963016 was highly similar to U.S.-Lantus notwithstanding minor differences in clinically inactive components, and that there were no clinically meaningful differences between LY2963016 and U.S.-Lantus in terms of the safety, purity, and potency of the product (see BMER dated December 17, 2021). The Agency concluded that the information submitted by the Applicant demonstrated that LY2963016 was biosimilar to U.S.-Lantus for each of the following indications for which U.S.-Lantus had been previously approved and for which the Applicant was seeking licensure of LY2963016: to improve glycemic control in adults and pediatric patients with type 1 diabetes and in adults with type 2 diabetes mellitus.

Additionally, consistent with section 351(k)(4) of the PHS Act, the data and information provided by the Applicant were sufficient to support a scientific conclusion that LY2963016 could be expected to produce the same clinical result as the reference product in any given patient and that the risk in terms of safety or diminished efficacy of alternating or switching between use of LY2963016 and U.S.-Lantus was not greater than the risk of using U.S.-Lantus without alternation or switch.

However, the application was submitted under section 351(k) of the PHS Act and relied on the same reference product for which a prior biological product had received a determination of interchangeability on July 28, 2021. The application was therefore a second or subsequent biological product as described in section 351(k)(6) of the PHS Act. Pursuant to section 351(k)(6), FDA shall not make a determination under section 351(k)(4) of the PHS 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. Therefore, a determination of interchangeability under 351(k)(4) could not made for the 351(k) application for LY2963016 at that time.

As a result, the Agency split the application for administrative purposes, as follows:

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

On December 17, 2021, the Agency approved BLA 761215/Original 1 as a biosimilar to U.S.-Lantus, and issued a complete response letter (CRL) for BLA 761215/Original 2 informing the Applicant of the foregoing determination regarding interchangeability and our rationale.

On June 7, 2022, FDA approved updated labeling for U.S.-licensed Lantus, including an update to the Indications and Usage section to the following: to improve glycemic control in adult and pediatric patients with diabetes mellitus.

Clinical Review Considerations, Rationale, and Conclusions:

On May 16, 2022, the Applicant provided a complete response to the CRL issued on December 17, 2021 in this BLA/Original 2 resubmission for Rezvoglar (insulin glargine-aglr) as a proposed interchangeable biosimilar with U.S.-licensed Lantus. The submission contains a note to the reviewer with the complete response, U.S. Prescribing Information (revised to contain interchangeability wording) and corresponding Structured Product Labeling, a quality overall summary, and a safety update. No other information was provided as the Applicant notes that there were no analytical, nonclinical, clinical, or chemistry, manufacturing, and controls (CMC) deficiencies identified in the CRL.

In the submission, the Applicant notes that the first interchangeable exclusivity for the first interchangeable biosimilar to U.S.-licensed Lantus expires on November 15, 2022. The Applicant states the analytical, nonclinical and clinical data that were relied upon to support the initial review of LY2963016 as interchangeable with U.S.-licensed Lantus remain unchanged. Additionally, the CMC data continues to support that the facility where Rezvoglar is manufactured, processed, packed or held meets standards designed to assure that it continues to be safe, pure and potent.[1]

[1] Of note, a CMC supplement was submitted to BLA 761215 on May 9, 2022 (Supplement 1, SDN 22). (b) (4) BLA 761215 S-001 (b) (4) was approved on September 1, 2022. The aforementioned process changes did not have an impact on the product quality of the Rezvoglar DS/drug product (DP); the resultant Rezvoglar DS/DP is comparable to the Rezvoglar DS/DP approved in the original BLA. Accordingly, the Agency's previous conclusions with respect to biosimilarity of Rezvoglar to U.S.-Lantus, and the Agency's previous scientific conclusions that LY2963016 could be expected to produce the same clinical result as the reference product in any given patient and that the risk in terms of

In the submitted clinical safety update, the Applicant states that Rezvoglar has not yet entered the U.S. market and no new clinical studies of LY2963016 as Rezvoglar have been conducted. However, the Applicant has included safety update data for Basaglar (an insulin glargine product), (b) (4) The Applicant holds the license for Basaglar. The safety update includes a list of studies completed since the original BLA 761215 submission, consisting of one nonclinical study evaluating LY2963016 and three clinical studies evaluating Basaglar. The safety update also includes a summary of the Applicant's findings after review of the postmarket safety data and literature for Basaglar. Finally, the Applicant submitted a Periodic Safety Update Report (PSUR) for LY2963016 covering the reporting period of April 22, 2020 through April 21, 2021. No new safety signals were identified for LY2963016 during the reporting period.

In considering the data submitted in the original BLA 761215/Original 2 and the data submitted in this resubmission, the Applicant has provided data and information sufficient to maintain FDA's scientific conclusion that Rezvoglar can be expected to produce the same clinical result as the reference product in any given patient and that the risk in terms of safety or diminished efficacy of alternating or switching between use of Rezvoglar and U.S.-Lantus is not greater than the risk of using U.S.-Lantus without alternation or switch.

Therefore, our recommendation is for approval of Rezvoglar as an interchangeable biosimilar to U.S.-Lantus for the following indication, for which U.S.-Lantus has been previously approved and for which the Applicant is seeking licensure: to improve glycemic control in adult and pediatric patients with diabetes mellitus.

Labeling Review:

The Applicant's resubmission included labeling only for the proposed United States Prescribing Information (USPI). As noted above on June 7, 2022, FDA approved updated labeling for U.S.-licensed Lantus, including an update to the Indications and Usage section to the following: to improve glycemic control in adult and pediatric patients with diabetes mellitus.

On July 20, 2022, the Agency sent an information request to the Applicant informing them of the updated reference product labeling and instructing them to revise the draft Rezvoglar labeling pieces (Prescribing Information, Patient Information, and Instructions for Use) to align with the U.S.-licensed Lantus labeling approved on June 7, 2022, and submit the revised labeling to the 351(k) application for review. On August 19, 2022, the Applicant submitted updated labeling aligned with the revised U.S.-licensed Lantus labeling.

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safety or diminished efficacy of alternating or switching between use of LY2963016 and U.S.-Lantus was not greater than the risk of using U.S.-Lantus without alternation or switch, continue to be valid.

Our review concluded that the proposed Rezvoglar labeling is compliant with the Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), is consistent with CDER/OND best labeling practices and policies, is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product.

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/

ANN J MILLER
11/03/2022 03:17:53 PM

MICHELLE CAREY
11/03/2022 03:19:37 PM