BLA 761109

BLA APPROVAL

Eli Lilly and Company
Attention: Christine A. Phillips, Ph.D., RAC
Advisor, Global Regulatory Affairs,
North America Diabetes
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Phillips:

Please refer to your biologics license application (BLA) dated and received August 15, 2019, and your amendments, submitted under section 351(a) of the Public Health Service Act for Lyumjev (insulin lispro-aabc) injection.

We also refer to our approval letter dated June 15, 2020, which contained the following error: The PREA partial waivers were not included under the Required Pediatric Assessments section.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain June 15, 2020, the date of the original approval letter.

LICENSING

We have approved your BLA for Lyumjev (insulin lispro-aabc) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Lyumjev under your existing Department of Health and Human Services U.S. License No. 1891. Lyumjev is indicated to improve glycemic control in adults with diabetes mellitus.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture insulin lispro-aabc drug substance at Lilly del Caribe, Inc. in Carolina, Puerto Rico and Eli Lilly and Company in Indianapolis, Indiana for purification and fill operations. The final formulated drug product will be manufactured and filled at Eli Lilly and Company in Indianapolis, Indiana. The vials will be labeled and packaged at Eli Lilly and Company in Indianapolis, Indiana. The cartridge and device will be labeled, packaged, and assembled at Eli Lilly and Company in Indianapolis, Indiana and Lilly France in Fegersheim, France. You may label your product with the proprietary name, Lyumjev, and market it in a pre-filled single-patient-use Tempo Pen (300 units/3 mL), Junior KwikPen (300 units/3 mL),

KwikPen (300 units/3 mL or 600 units/3 mL), in a multi-dose vial (1000 units/10 mL), or in a single-patient-use cartridge (300 units/3 mL).

DATING PERIOD

The dating period for Lyumjev shall be 24 months from the date of manufacture when stored at 2°C to 8°C. 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 protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Lyumjev 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 Lyumjev, or in the manufacturing facilities, will require the submission of information to your biologics license application 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, with minor editorial revisions listed below and reflected in the enclosed labeling.

Issue dates added to labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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, as described at

FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Patient Package, and Insert, Instructions for Use). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[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 *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761109**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Lyumjev was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from 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 studies requirement for type 1 diabetes mellitus in ages 0 to < 1 year and type 2 diabetes mellitus in ages 0 to < 10 years because necessary studies are impossible or highly impracticable. This is because there are too few children in this age range with diabetes mellitus to study.

We are deferring submission of your pediatric study for ages 1-17 years (inclusive) until June 2023, because this product is ready for approval for use in adults and the pediatric study has not been completed.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[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 study required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act is required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(4)(C) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

3874-1 Conduct a 26-week, randomized, controlled efficacy and safety study comparing Lyumjev (insulin lispro-aabc) administered at mealtime and Lyumjev (insulin lispro-aabc) administered 20 minutes postmeal to Humalog administered at mealtime, in combination with long acting insulin, in pediatric patients with type 1 diabetes ages 1 to 17 years (inclusive).

Study Completion: June 2022
Final Report Submission: June 2023

Submit the protocol(s) to your IND 127210, with a cross-reference letter to this BLA. Reports of this required pediatric postmarketing study must be submitted as a biologics license application (BLA) or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from this study. 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.

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*.[3]

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.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80).

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

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

You must submit distribution reports under the distribution reporting requirements for licensed biological products (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

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at FDA.gov.[6]

[6] http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm

If you have any questions, call Callie Cappel-Lynch, Regulatory Project Manager, at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

Patrick Archdeacon, M.D.
Associate Director for Therapeutics (Acting)
Division of Diabetes, Lipid Disorders, and Obesity
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURES:

- 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/

PATRICK ARCHDEACON
06/15/2020 12:00:00 AM