BLA 761355

BLA APPROVAL

Regeneron Pharmaceuticals, Inc.
Attention: Donato Forlenza, PharmD, MBa
Senior Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591

Dear Dr. Forlenza:

Please refer to your biologics license application (BLA) dated and received December 27, 2022, and your amendments, submitted under section 351(a) of the Public Health Service Act for Eylea HD (aflibercept) injection. We acknowledge receipt of your resubmission dated July 3, 2023, which constituted a complete response to our June 27, 2023, action letter.

We have completed our review of this application, as amended. Your BLA for Eylea HD is approved, effective on the date of this letter for use as recommended in the enclosed agreed-upon labeling with minor editorial revisions reflected in the enclosed labeling. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Eylea HD under your existing Department of Health and Human Services U.S. License No. 1760. Eylea HD is indicated for treatment of neovascular (wet) age-related macular degeneration (AMD), diabetic macular edema (DME), and diabetic retinopathy (DR).

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Eylea HD drug substance at Regeneron Pharmaceuticals, Inc., in Rensselaer, NY (FEI: 1000514603). The final formulated drug product will be manufactured and filled at (b) (4) and labeled and packaged at (b) (4) (b) (4) You may label your product with the proprietary name, Eylea HD, and market it as 8 mg (0.07 mL of 114.3 mg/mL solution) in a 2 mL glass vial.

DATING PERIOD

The dating period for Eylea HD 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) °C.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Eylea HD and each kit component 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 Eylea HD, 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.

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). 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 (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 761355**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Eylea HD was not referred to an FDA advisory committee because this biologic is not the first in its class.

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable. We are waiving the pediatric study requirement for this application

[1] See 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.

because necessary studies are impossible or highly impracticable as the conditions rarely or never occur in pediatrics.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4496-1 Perform [redacted] (b) (4)

The timetable you submitted on August 17, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 9/2023

4496-2 Perform real-world shipping studies on the final drug product in the proposed container closure system, covering worst case shipping conditions (i.e., routes and modes of transportation, distance, duration, temperature, packing configuration, and shipping containers employed) which includes an evaluation of product quality and microbial data as well as a comparison of pre-shipment to post shipment data, assessed against pre-defined acceptance criteria.

The timetable you submitted on August 17, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 3/2024

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]

[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

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

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

[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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.

If you have any questions, please contact Michael Puglisi, Regulatory Project Manager, at michael.puglisi@fda.hhs.gov or at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Director
Division of Ophthalmology
Office of Specialty Medicine
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
- 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/

WILEY A CHAMBERS
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