BLA 761298/Original 1

BLA APPROVAL

Amgen, Inc.
Attention: Amanda Santoro
Senior Manager, Global Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320

Dear Amanda Santoro:

Please refer to your biologics license application (BLA) dated and received August 23, 2023, and your amendments, submitted under section 351(k) of the Public Health Service Act for Pavblu (aflibercept-ayyh) injection.

This BLA provides for the licensure of Pavblu (aflibercept-ayyh) as follows:

- Pavblu (aflibercept-ayyh), 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a single-dose vial (vial) (b) (4) US-Eylea (aflibercept) 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a single-dose vial kit (vial kit) and single-dose pre-filled syringe (PFS), and

- Pavblu (aflibercept-ayyh), 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a PFS (b) (4) US-Eylea (aflibercept) 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a PFS.

Pavblu seeks licensure (b) (4) US-Eylea for the following indications:

- Neovascular (wet) age-related macular degeneration (AMD),
- Macular edema following retinal vein occlusion (RVO),
- Diabetic Macular Edema (DME), and
- Diabetic Retinopathy (DR).

For administrative purposes, we have split BLA 761298 into the following applications:

- BLA 761298/Original 1 – biosimilarity
    - Pavblu, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial and PFS seeking biosimilarity to US-Eylea 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial kit and PFS.

(b) (4)

(b) (4)

(b) (4)

LICENSING

We have approved your BLA for Pavblu (aflibercept-ayyh) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Pavblu under your existing Department of Health and Human Services U.S. License No. 1080. Pavblu is indicated for neovascular (wet) age-related macular degeneration (AMD), macular edema following retinal vein occlusion (RVO), diabetic macular edema (DME), and diabetic retinopathy (DR).

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Pavblu (aflibercept-ayyh) drug substance at Amgen Singapore Manufacturing Pte. Ltd., in Singapore 637026, Singapore. The final formulated product for the vial will be manufactured and filled at Amgen Inc., in Thousand Oaks, CA. The final formulated product for the vial will be labeled and packaged at Amgen Manufacturing Ltd., in Juncos, PR. The final formulated product for the PFS will be manufactured and filled at Amgen Manufacturing Limited, in Juncos, PR. The final formulated product for the PFS will be assembled, labeled, and packaged at (b) (4) You may label your product with the proprietary name, Pavblu, and market it as a 2 mg (0.05 mL of 40 mg/mL) solution in a vial, and as a 2 mg (0.05 mL of 40 mg/mL) solution in a PFS assembled with a non-retractable plunger rod and a backstop flange extender.

DATING PERIOD

The dating period for Pavblu vial shall be 36 months from the date of manufacture when stored at 2°C to 8°C, with a single room temperature storage period of up to 3 days at a maximum of 30°C, and the dating period for Pavblu PFS shall be 24 months from the date of manufacture when stored at 2°C to 8°C, with a single room temperature storage period of up to 3 days at a maximum of 30°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)

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Pavblu 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 Pavblu, 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.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

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 761298/Original 1**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

[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.

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 have determined that, at this time, no pediatric studies will be required under PREA for your BLA.

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

We remind you of your postmarketing commitments:

4688-1 Perform real-time ABP938 pre-filled syringe (PFS) drug product commercial container closure system leachate studies using appropriate test methods to identify and quantify volatile organic compounds (VOC), semi-VOC, non-VOC and trace metals at regular intervals through the end of shelf-life. The final results of this study and the toxicology risk evaluation for the levels of leachates detected in the drug product will be provided in the final study report to the BLA.

The timetable you submitted on June 17, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 02/2026

4688-2 Perform a validation study for a suitable method for (b) (4) testing and add (b) (4) testing as an in-process control (IPC) test with acceptance criterion for ABP938 drug substance manufacture. Data and information to support method validation and the IPC limit will be provided in a Changes Being Effected in 30 days (CBE-30) by February 2025.

Conduct (b) (4) testing on the first 30 ABP938 drug substance lots manufactured and re-evaluate the proposed (b) (4) IPC limit based on the drug substance manufacturing data.

The timetable you submitted on August 12, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 02/2025

Submit clinical protocols to your IND 135489 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to

this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

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 601.12(f)(4)]. 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 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:

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[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

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

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 Ahmed Ayodeji, PharmD, Regulatory Project Manager, at Ahmed.Ayodeji@fda.hhs.gov, or call (301) 837-7390.

Sincerely,

{See appended electronic signature page}

William Boyd, MD
Deputy Director
Division of Ophthalmology
Office of Specialty Medicine
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- 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/

WILLIAM M BOYD
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