BLA 761269

BLA ACCELERATED APPROVAL

Eisai Inc.
Attention: Stacie P. O'Sullivan
Director, Global Regulatory Strategy
200 Metro Boulevard
Nutley, NJ 07110

Dear Ms. O'Sullivan:

Please refer to your biologics license application (BLA) dated and received on May 6, 2022, submitted under section 351(a) of the Public Health Service Act for Leqembi (lecanemab-irmb) injection.

LICENSING

We have approved your BLA for Leqembi (lecanemab-irmb) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Leqembi (lecanemab-irmb) under your existing Department of Health and Human Services U.S. License No. 1862. Leqembi is indicated for the treatment of Alzheimer's disease.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture lecanemab-irmb drug substance at (b) (4) The final formulated product will be manufactured, filled, labeled, and packaged at Biogen U.S. Corporation, Research Triangle Park, North Carolina. You may label your product with the proprietary name Leqembi and will market it in 200 mg/2 mL (100 mg/mL) or 500 mg/5 mL (100 mg/mL) injection.

DATING PERIOD

The dating period for Leqembi shall be 12 months from the date of manufacture when stored at 2-8 °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 Leqembi 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 Leqembi, 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 AND LABELING

We have completed our review of this application. It is approved under accelerated approval pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act (FDCA) and 21 CFR 601.41, effective on the date of this letter, for use as recommended in the enclosed agreed-upon approved labeling. This BLA provides for the use of Leqembi for the treatment of Alzheimer's disease.

Marketing of this drug product and related activities must adhere to the substance and procedures of the accelerated approval statutory provisions and regulations.

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 and Medication Guide). Information on submitting SPL files using eLIST may be found in the draft 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.

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[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

[2] When final, this guidance will represent FDA's current thinking on this topic. We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the submitted carton and container labeling, except with the minor revisions listed above [e.g., changes consistent with annual reportable changes under 21 CFR 601.12(d)], 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 (April 2018, Revision 5)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761269**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Leqembi was not referred to an FDA advisory committee because this biologic did not raise new or unexpected safety or efficacy issues for a drug of this class.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under accelerated approval pursuant to section 506(c) of the FDCA and 21 CFR 601.41 may require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If required postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated December 16, 2022. This requirement, along with required completion dates, is listed below.

4384-1: In order to verify the clinical benefit of lecanemab-irmb, conduct a randomized, controlled trial to evaluate the efficacy of lecanemab-irmb compared to an appropriate control for the treatment of Alzheimer's disease. The trial should be of sufficient duration to observe changes on an acceptable endpoint in the patient population enrolled in the trial.

Draft Protocol Submission:	10/2018 (submitted)
Final Protocol Submission:	04/2019 (submitted)
Trial Completion:	09/2022
Final Report Submission:	03/2023

Submit clinical protocols to your IND 105081 for this product. In addition, you must submit status reports of the progress of each requirement not later than 180 days after the date of approval of this drug and every 180 days thereafter (section 506(B)(a) of the FDCA as amended by section 3210(b) of the Food and Drug Omnibus Reform Act of

2022). The status summary should include expected trial completion and final report submission dates, any changes in plans since the last report, and, for clinical trials, the number of patients entered into each trial (21 CFR 601.70).

Submit final reports to this BLA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart E Postmarketing Requirement(s)**."

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 study requirement for this application because necessary studies are impossible or highly impracticable, as Alzheimer's disease only occurs in the adult population.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of immunogenicity.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

4384-2: Improve the sensitivity for the current anti-drug antibody (ADA) assay to at least 100 ng/mL in the presence of the trough level of drug expected to be present during sampling. If sensitivity for the current ADA assay cannot be improved, develop and validate an alternative assay with this level of sensitivity. Improve the sensitivity and drug tolerance for the current neutralizing antibody (NAb) assay. If sensitivity and drug tolerance for the

current NAb assay cannot be improved, develop and validate an alternative assay with adequate sensitivity and drug tolerance. Include in the assay validation a statistical evaluation of distribution and outlier exclusion for cutpoint samples, selectivity, system suitability specifications for negative and positive controls, and effects of hemolysis. Refer to the 2019 FDA guidance for immunogenicity assays (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/immunogenicity-testing-therapeutic-protein-products-developing-and-validating-assays-anti-drug), as this document recommends sensitivity in the range of 100 ng/mL or lower.

The timetable you submitted on December 16, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 06/2023
Final Protocol Submission: 09/2023
Study Completion: 11/2023
Final Report Submission: 01/2024

4384-3: Using the improved and validated assays developed in response to PMR 4384-2, evaluate the impact of ADA and NAb on the pharmacokinetics, pharmacodynamics, safety, and efficacy of lecanemab-irmb in patients enrolled in the confirmatory study.

The timetable you submitted on December 16, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 01/2024
Final Protocol Submission: 04/2024
Study Completion: 04/2025
Final Report Submission: 06/2025

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit clinical protocol(s) to your IND 105081 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o)**.

[3] See the guidance for Industry Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019). https://www.fda.gov/RegulatoryInformation/Guidances/default htm.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 601.70, include a requirement to report annually on the status of any required studies or clinical trials under section 505(o)(3).

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

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

We remind you of your postmarketing commitment:

4384-4: Perform a shipping study to confirm validation of the commercial lecanemab-irmb drug product shipping conditions and provide the results of your study. The study will include monitoring of temperature during the shipment, testing of pre- and post-shipping samples for product quality (purity by SEC, cSDS reduced and non-reduced, cIEF, sub-visible particles, and potency of lecanemab-irmb), and confirmation that the commercial shipping configuration minimizes physical damage to drug product containers.

The timetable you submitted on December 16, 2022, states that you will conduct this study according to the following schedule:

Study/Trial Completion: 07/2023
Final Report Submission: 08/2023

Submit clinical protocols to your IND 105081 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**."

REQUESTED PHARMACOVIGILANCE

We request expedited reporting of any deaths in ongoing studies and of deaths resulting from cerebral hemorrhage greater than 1 centimeter in size in the postmarketing setting.

We request that you perform postmarketing pharmacovigilance to characterize the risk of ARIA and the monitoring for ARIA associated with the use of Leqembi. Please provide biannual reports of ARIA-E and ARIA-H (specifying microhemorrhage or superficial siderosis), along with any incident cerebral hemorrhage greater than 1 centimeter in size. Provide a synthesized summary and analysis, including incidence of clinical trial cases, postmarketing cases, and total cases. Include an evaluation of central nervous system hemorrhage in patients with pre-existing risk factors for bleeding, including concomitant medications that could increase the risk for bleeding. Include an analysis that addresses the monitoring recommendations provided for in the prescribing information. The summary should provide an analysis for all subjects and a separate analysis for those in the United States and for those in the rest of the world. For each case, provide line listings that include:

- Case ID
- Whether the case was a clinical trial case, postmarketing spontaneous report, or postmarketing from a registry
- Age
- Alzheimer's disease stage
- Patient characteristics, including ApoE ε4 genotype if available
- Country where patient is treated
- Concomitant medications
- Time from first Leqembi dose to ARIA
- Listing of dates of Leqembi dosing
- Dates of MRI, including baseline MRI
- Description of MRI findings, including baseline MRI
- Whether patient was symptomatic and if so, list symptoms
- Whether initial finding was symptom or MRI
- Patient outcome (e.g., death, permanent disability, resolved)
- Date of resolution of MRI and of symptoms
- Whether the patient was hospitalized
- Whether and what treatment was received for ARIA
- Whether Leqembi was held, and date that Leqembi dosing resumed
- Whether Leqembi was discontinued
- Specialty of the prescribing physician (e.g., neurologist, psychiatrist, internist)

We request that you perform postmarketing pharmacovigilance and provide biannual reports to identify and analyze cases of vasculitis that occur after use of Leqembi.

We request that you perform postmarketing pharmacovigilance to characterize the risk of infusion reactions associated with the use of Leqembi. Please provide biannual reports of serious infusion reactions, including line listings of the cases, FAERS reports, and a synthesized summary and analysis including incidence of clinical trial cases, postmarketing cases, and total cases.

PROMOTIONAL MATERIALS

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

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*.[4]

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.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

[4] https://www.fda.gov/media/128163/download

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

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, contact E. Andrew Papanastasiou, Regulatory Project Manager, by email at emilios.papanastasiou@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Director
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide

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/

TERESA J BURACCHIO on behalf of WILLIAM H Dunn
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