BLA 761178

**BLA ACCELERATED APPROVAL**

Biogen Inc.
Attention: Priya Singhal, MD, MPH
Vice President, Global Safety and Regulatory Sciences
225 Binney Street
Cambridge, MA 02142

Dear Dr. Singhal:

Please refer to your biologics license application (BLA) dated and received on July 7, 2020, and your amendments, submitted under section 351(a) of the Public Health Service Act for Aduhelm (aducanumab-avwa) injection.

We acknowledge receipt of your major amendment dated January 27, 2021, which extended the goal date by three months.

## LICENSING

We have approved your BLA for Aduhelm (aducanumab-avwa), effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce Aduhelm under your existing Department of Health and Human Services U.S. License No. 1697. Aduhelm is indicated for the treatment of Alzheimer's disease.

## MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Aduhelm drug substance at Biogen MA, Inc., in Research Triangle Park, North Carolina, USA. The final formulated product will be manufactured and filled at (b) (4) and Biogen U.S. Corporation, Research Triangle Park, North Carolina, USA. The final formulated product will be labeled and packaged at (b) (4) You may label your product with the proprietary name, Aduhelm, and will market it in a single-use vial (170 mg/1.7 mL or 300 mg/3 mL injection).

## DATING PERIOD

The dating period for Aduhelm shall be 30 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) °C.

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 Aduhelm 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 Aduhelm, 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, as amended. It is approved under the provisions of accelerated approval regulations (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 Aduhelm for the treatment of Alzheimer's disease.

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

[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 carton and container labeling submitted on October 30, 2020, 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 (February 2020, Revision 7)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761178**." Approval of this submission by FDA is not required before the labeling is used.

## ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 601.41, 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 postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43(b), withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated May 28, 2021. This requirement, along with required completion dates, is listed below.

3971-1: In order to verify the clinical benefit of aducanumab, conduct a randomized, controlled trial to evaluate the efficacy of aducanumab-avwa 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.

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| Draft Protocol Submission: | 10/2021 |
| Final Protocol Submission: | 08/2022 |
| Trial Completion: | 08/2029 |
| Final Report Submission: | 02/2030 |

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.

Submit clinical protocols to your IND 106230 for this product. In addition, under 21 CFR 601.70, you should include a status summary of each requirement in your annual report 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 entered into each study/trial.

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 COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3971-2: Perform shipping qualification studies for drug product and finished goods.

The timetable you submitted on June 4, 2021, states that you will conduct this study according to the following schedule:

Final Report Submission: 02/2022

3971-3: Implement a validated product-specific host cell protein (HCP) assay in the aducanumab drug substance manufacturing process. Submit the HCP method and method validation report in a supplement within 9 months of licensure.

The timetable you submitted on June 4, 2021, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2022

3971-4: Evaluate matrix interference from hemolysis and lipidemia in the aducanumab anti-drug antibody assay.

The timetable you submitted on June 4, 2021, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2021

3971-5: Provide the KTA bacterial endotoxin test method qualification data from Biogen US Corporation and submit the report as a CBE-0.

The timetable you submitted on June 4, 2021, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2021

3971-6: Implement the bacterial endotoxins test for the (b) (4) and submit as the final report as a CBE-0.

The timetable you submitted on June 4, 2021, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2021

Submit clinical protocols to your IND 106230 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 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**."

## RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

We acknowledge receipt of your submission dated July 7, 2020, of a proposed risk evaluation and mitigation strategy (REMS). We have determined that, at this time, a REMS is not necessary for Aduhelm to ensure that its benefits outweigh its risks. We will notify you if we become aware of new safety information and make a determination that a REMS is necessary.

## REQUESTED PHARMACOVIGILANCE

We request that you perform postmarketing pharmacovigilance to characterize the risk of ARIA and monitoring for ARIA associated with the use of Aduhelm. 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 the registry
- Age
- Alzheimer's disease stage
- Patient characteristics, including APOε4 genotype if available
- Country where patient is treated
- Concomitant medications
- Time from first Aduhelm dose to ARIA
- Listing of dates of Aduhelm dosing
- Dates of MRI
- Description of MRI findings
- Whether patient was symptomatic and if so, list symptoms
- Whether initial finding was symptom or MRI
- Date of resolution of MRI and of symptoms
- Whether the patient was hospitalized
- Whether and what treatment was received for ARIA
- Whether Aduhelm was held, and date that Aduhelm dosing resumed
- Whether Aduhelm was discontinued
- Specialty of the prescribing physician (e.g., neurologist, psychiatrist, internist)

We request that you perform postmarketing pharmacovigilance to characterize the risk of hypersensitivity associated with the use of Aduhelm. Please provide biannual reports of serious hypersensitivity 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*.[3]

## 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).

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

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

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

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**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.**

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/s/

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WILLIAM H Dunn
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