DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761077

BLA APPROVAL

Amgen, Inc.
Attention: Vanessa Shurn
601 13th Street, N.W.
Washington, D.C. 20005

Dear Ms. Shurn:

Please refer to your Biologics License Application (BLA) dated and received May 17, 2017, and your amendments, submitted under section 351(a) of the Public Health Service Act for Aimovig (erenumab-aooe) injection 70 mg/mL.

We also refer to our approval letter dated May 17, 2018, which contained the following error: omission of the Prescribing Information.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain May 17, 2018, the date of the original approval letter.

LICENSING

We have approved your BLA for Aimovig (erenumab-aooe) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce Aimovig under your existing Department of Health and Human Services U.S. License No. 1080. Aimovig is indicated for the preventive treatment of migraine in adults.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture erenumab-aooe drug substance at Amgen Thousand Oaks in Thousand Oaks, California. The final formulated drug product will be manufactured, filled, labeled, and packaged at Amgen Manufacturing Limited, Juncos, Puerto Rico. You may label your product with the proprietary name Aimovig, and market it in a prefilled syringe 70 mg/mL and autoinjector 70 mg/mL.

DATING PERIOD

The dating period for Aimovig shall be 24 months from the date of manufacture when stored at 2-8°C and protected from light. 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.

Results of ongoing stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Aimovig to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2a. 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 Aimovig, 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, for use as recommended in the enclosed agreed-upon labeling text.

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 [21 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your submissions dated December 1, 2017, and May 11, 2018, containing final printed carton and container labels.

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 children 0 to 5 years of age. In children 0 to 5 years of age, clinical studies for the preventive treatment of migraine would be highly impracticable because very few children of this age can be definitively diagnosed with migraine and even fewer would be candidates for preventive therapy.

We are deferring submission of your pediatric studies for children 6 to 17 years of age for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually, according to 21 CFR 601.28 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

PMR 3392-1 Juvenile monkey toxicology study to evaluate effects of erenumab-aooe on growth, reproductive development, and neurological and neurobehavioral development.

Draft protocol submission: Submitted 01/2017
Final protocol submission: 05/2018
Study completion: 06/2019
Final report submission: 09/2019

PMR 3392-2 An open-label pharmacokinetic, safety, and tolerability study in pediatric migraine patients ages 6 through 11 years. Dosing will depend on body weight, according to two weight bands: <40 kg and ≥40 kg. The study should identify doses that provide exposures that match those observed with the 70-mg and 140-mg doses of Aimovig in adults.

Draft protocol submission: Submitted 06/2017
Final protocol submission: Submitted 12/2017
Study completion: 12/2021
Final report submission: 12/2025

PMR 3392-3 Deferred pediatric randomized, double-blind, placebo-controlled efficacy and safety study under PREA for the preventive treatment of chronic migraine in adolescents ages 12 through 17 years. This study includes a double-blind treatment phase (of at least 12 weeks duration), with an open-label extension (of

at least 40 weeks duration). Two weight bands should be utilized for dosing. In each weight band, two different dosing levels of Aimovig should be tested. Dosing should provide exposures matching those observed with the 70-mg dose and with the 140-mg dose of Aimovig in adults. This study is to be submitted as a special protocol assessment (SPA).

Final protocol submission: 03/2019
Study completion: 06/2025
Final report submission: 12/2025

PMR 3392-4 Deferred pediatric randomized, double-blind, placebo-controlled efficacy and safety study under PREA for the preventive treatment of episodic migraine in children and adolescents ages 6 through 17 years. This study includes a double-blind treatment phase (of at least 12 weeks duration), with an open-label extension (of at least 40 weeks duration). Two weight bands should be utilized for dosing. In each weight band, two different dosing levels of Aimovig should be tested. Dosing should provide exposures matching those observed with the 70-mg dose and with the 140-mg dose of Aimovig in adults. This study is to be submitted as a special protocol assessment (SPA).

Final protocol submission: 03/2019
Study completion: 06/2024
Final report submission: 12/2025

Submit the protocols to your IND 116,098, with a cross-reference letter to this BLA.

Reports of these required pediatric postmarketing studies must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. 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.

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 adverse maternal, fetal, and infant outcomes resulting from the use of Aimovig (erenumab) during pregnancy.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

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

PMR 3392-5 Conduct prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with migraine exposed to Aimovig during pregnancy with two unexposed control populations: one consisting of women with migraine who have not been exposed to Aimovig before or during pregnancy and the other consisting of women without migraine. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

The timetable you submitted on April 20, 2018, states that you will conduct this study according to the following schedule:

Draft protocol submission:	12/2018
Final protocol submission:	05/2019
Annual Interim Report Submissions:	
	07/2020
	07/2021
	07/2022
	07/2023
	07/2024
	07/2025
Study Completion:	07/2026
Final Report Submission:	07/2027

PMR 3392-6 Conduct a pregnancy outcomes study using a different study design than provided for in PMR 3392-5 (for example, a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small-for-gestational-age births in women exposed to Aimovig during pregnancy compared to an unexposed control population.

The timetable you submitted on April 20, 2018, states that you will conduct this study according to the following schedule:

Draft protocol submission:	10/2018
Final protocol submission:	03/2019

Annual Interim Report Submissions:	
	05/2020
	05/2021
	05/2022
	05/2023
	05/2024
	05/2025
	05/2026
Study Completion:	05/2026
Final Report Submission:	05/2027

Submit clinical protocols to your IND 116,098, with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports 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).**

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

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 of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B 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.

REQUESTED PHARMACOVIGILANCE

We request that you perform postmarketing surveillance for liver toxicity, myocardial infarction, and stroke after exposure to Aimovig. Include comprehensive summaries and analyses of these events quarterly as part of your required postmarketing safety reports [e.g., periodic safety update reports (PSURs)]. Include analyses of the events by age and gender. In the analysis of each case, provide an assessment of causality, with documentation of risk factors and results of

all assessments that support the diagnosis or the causality, along with duration of erenumab therapy, concomitant therapies, treatment given for the event, and outcome. Include a comparison to background rates expected in a migraine population of the same age and gender.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

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

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

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 4206
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, call Lana Chen, Regulatory Project Manager, at (301) 796-1056.

Sincerely,

{See appended electronic signature page}

Ellis Unger, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling (PI, PPI and IFUs)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLIS F UNGER
05/17/2018