BLA 761333/S-003

SUPPLEMENT APPROVAL

Amgen Inc.
Attention: Augustus Kamassah
Director, Global Biosimilars Regulatory Affairs
One Amgen Center Drive, Mail Stop: 28-4A
Thousand Oaks, CA 91320

Dear Augustus Kamassah:

Please refer to your supplemental biologics license application (sBLA), dated and received December 20, 2024, submitted under section 351(k) of the Public Health Service Act for Bkemv (eculizumab-aeeb) injection.

This Changes Being Effected supplemental sBLA provides for proposed modifications to the approved Bkemv risk evaluation and mitigation strategy (REMS).

We have completed our review of this supplemental application. It is approved effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Bkemv was originally approved on May 28, 2024, and the most recent REMS modification was approved on October 23, 2024. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modifications to the REMS, consist of adding the option for online certification and enrollment for healthcare settings and pharmacies.

Your proposed modified REMS, submitted on December 20, 2024, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on May 28, 2024.

The revised REMS assessment plan must include, but is not limited to, the following:

For each metric, provide the 2 previous, current, and cumulative reporting periods (where applicable) unless otherwise noted.

Program Implementation and Operations

1. REMS Implementation (for the first REMS assessment only)

    a. Date of first commercial distribution of BKEMV

    b. Date of BKEMV REMS launch

    c. Date when the BKEMV REMS website became live and fully operational

    d. Date when healthcare providers (HCPs) who can prescribe could become certified in the BKEMV REMS

    e. Date when healthcare settings and pharmacies could become certified in the BKEMV REMS

    f. Date when wholesalers-distributors were authorized to distribute the drug (i.e., first order placed)

    g. Date of first healthcare prescriber certification

    h. Date of first healthcare setting and pharmacy certification

    i. Date when the REMS Coordinating Center was established and fully operational

2. REMS Certification and Enrollment Statistics

    a. Healthcare provider (HCP) certification

        i. The number of HCPs certified: total, newly certified, and active (prescribed BKEMV at least once during the reporting period) stratified by credentials (e.g., Doctor of Medicine, Doctor of Osteopathic Medicine, Advanced Practice Registered Nurse, Physician Assistant), medical specialty (e.g., Hematology/Oncology, Immunology, Internal Medicine, Nephrology, Neurology, Rheumatology, and Other), and geographic region (as defined by US Census)

        ii. Method of certification (e.g., fax, online, email)

        iii. The number of HCPs who were unable to become certified, accompanied by a summary of the reason(s) why they were unable to be certified

    b. Healthcare Setting and Pharmacy Certification

i. The identity and numbers of each pharmacy and healthcare setting certified: total, newly certified and active (dispensed BKEMV at least once during the reporting period) stratified by type of pharmacy or healthcare setting (e.g., hospital, specialty, pharmacy) and geographic region (as defined by US Census)

ii. Method of healthcare setting and pharmacy certification (e.g., fax, online, email)

iii. The number of healthcare settings and pharmacies that were unable to become certified, accompanied by a summary of the reason(s) why they were unable to be certified

c. Wholesalers-distributors

i. Numbers contracted: total and newly contracted, and active (distributed BKEMV at least once during the reporting period)

3. Patient statistics

a. The number and percent of new patients treated with BKEMV

b. The number of patients treated with BKEMV stratified by sex, age, diagnosis, and geographic region (as defined by US Census)

4. BKEMV Utilization Data

a. The number of BKEMV shipments sent to healthcare settings and pharmacies, overall and stratified by quantity per shipment, and by geographic region (as defined by US Census)

b. For certified healthcare settings and pharmacies, the number of prescriptions dispensed stratified by:

i. Prescriber specialty, degree/credentials, and geographic region

ii. Patient demographics (e.g., age, sex), and geographic region (as defined by US Census)

iii. Whether the prescription was new or a refill

c. Percentage (%) of BKEMV dispenses corresponding to prescriptions written by REMS certified HCPs

d. The number of prescriptions not dispensed, accompanied by a listing and summary of all reasons for not dispensing the prescription (e.g., HCP not certified, REMS related issue)

e. For wholesalers-distributors, the number of orders distributed

5. REMS Compliance

a. A summary report of noncompliance identified, associated corrective and preventive action (CAPA) plans, and the status of CAPA plans. Provide a summary of noncompliance identified, including, but not limited to:

i. A copy of the noncompliance plan, including the criteria for determination of noncompliance for each stakeholder, actions taken to address noncompliance for each case, and what events led to suspension or decertification from the REMS

ii. The number of instances of noncompliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of noncompliance, the following information will be reported:

a) The unique ID(s) of the stakeholder(s) associated with the noncompliance event or deviation to enable tracking over time

b) The source of the noncompliance data

c) The results of root cause analysis

d) The action(s) taken in response to noncompliance

iii. The number and percentage of prescribers who prescribed BKEMV but were not certified

iv. The specific reasons why prescribers were not certified at the time of prescribing (i.e., emergency use, etc), and whether these prescribers subsequently became certified

v. The number and percentage of healthcare settings and pharmacies who obtained BKEMV that were not certified

vi. The specific reasons for the drug distributions to healthcare settings and pharmacies that were not certified

vii. The number of healthcare settings and pharmacies who became decertified, accompanied by a summary of reasons for decertification

6. Audits: Summary of audit activities including but not limited to:

a. A copy of the audit plan used for each audited stakeholder (i.e., healthcare settings, pharmacies, REMS Call Center)

b. The number of audits expected, and the number of audits performed for each stakeholder

c. The number and category of observations noted, stratified by category

d. A unique ID for each stakeholder that had observations to track observations by stakeholder over time

e. Documentation of completion of training for relevant staff

f. A summary report of documented processes and procedures for complying with the REMS requirements including how certified pharmacies obtain patient vaccination status from HCPs

g. Verification that at each audited healthcare setting and pharmacy location, the designated authorized representative is up to date. If not, include the number of new authorized representatives and verification of the site's recertification

h. Describe any corrective actions taken for any noncompliance (audit observation) identified during the audits as well as any preventative measures that were developed from uncovering these noncompliance events

    i. For those with deficiencies noted, report the number that successfully completed a CAPA plan by the due date

    ii. For any that did not complete the CAPA by the due date, describe additional actions taken

7. REMS Infrastructure and Performance

    a. REMS Website

        i. The number of visits and unique visits to the REMS website

        ii. The number of REMS materials downloaded or printed for each material

    b. REMS Coordinating Center Report

        i. The number of contacts by stakeholder type (patient/caregiver, healthcare provider, pharmacy, etc)

ii. A table summarizing the reasons for calls (e.g., certification question) by stakeholder type

iii. If the reason for the call(s) indicates a complaint, provide details on the nature of the complaint(s) and whether they indicate potential REMS burden or patient access issues

iv. A summary report of corrective actions resulting from issues identified

Safe Use Behaviors

8. Safe Use Behaviors
   Determination of patients' vaccination and antibacterial drug prophylaxis compliance is made using data collected via the certified healthcare settings and pharmacies documenting the patient's vaccination status.

   a. Methods utilized to determine whether or not patients received meningococcal vaccinations in accordance with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for patients receiving a complement inhibitor. Include vaccine serogroup, dosing (i.e., first vaccine dose, second vaccine dose and booster doses), and timing of the vaccinations, when the information is provided.

   b. Data on the number and percentage of new patients treated with BKEMV who report receiving meningococcal vaccination(s) out of the total number of patients who received BKEMV. Of those who reported receiving meningococcal vaccinations, provide the number and percentage of patients who:

      i. Received vaccinations in accordance with the most current ACIP recommendations for meningococcal vaccinations in patients receiving a complement inhibitor

      ii. Did not receive vaccinations in accordance with the most current ACIP recommendations for meningococcal vaccinations in patients receiving a complement inhibitor

   c. Data on the number and percentage of new patients treated with BKEMV who reported not receiving meningococcal vaccination(s) out of the total number of patients who received BKEMV

   d. Whether the patient received antibacterial drug prophylaxis, and timing of antibacterial drug prophylaxis in relation to the dosing of BKEMV (if available)

e. If any of the above information is missing, the reasons why this information is missing such as:

   i. Healthcare provider records do not include this information

   ii. Healthcare provider declined to provide information

   iii. Healthcare provider did not respond to healthcare setting/pharmacy queries

f. The number and percentage of patients dispensed BKEMV who received at least one dose of meningococcal vaccines (against all of the following serogroups: A, C, W, Y, and B) according to the most current ACIP recommendations in patients receiving a complement inhibitor and antibacterial drug prophylaxis, if needed, before the first dispense

g. The number and percentage of new patients treated with BKEMV who completed or were up to date with meningococcal vaccinations (against all of the following serogroups: A, C, W, Y, and B) as per the most current ACIP recommendations in patients receiving a complement inhibitor at the time of first dose

h. For patients who were not initially up to date with meningococcal vaccines when starting treatment, report the number and percentage who, up to 6 months after the first dose:

   i. Completed meningococcal vaccines

   ii. Did not complete meningococcal vaccines but were receiving antibacterial drug prophylaxis

   iii. Vaccination status was unknown after completed follow-up attempts

Health Outcomes and/or Surrogates of Health Outcomes

9. Summary of cases of meningococcal infections in patients receiving BKEMV

   a. For US cases, cases are summarized as follows:

      i. In the most recent Periodic Safety Update Report (PSUR) submitted to the BKEMV Biologics License Application (BLA) with a link to that PSUR corresponding with the reporting interval

      ii. Cumulative listing of all cases of meningococcal infections from approval to include cases identified during the current reporting period

b. For each US case, provide the following information:

   i. MedWatch or other case report number

   ii. Date of event and date of report to FDA

   iii. Patient age, race and sex

   iv. Indication for BKEMV treatment

   v. Meningococcal vaccination status

      a) Date of vaccine(s) (i.e., all of the meningococcal vaccines doses (serogroups: A, C, W, Y, and B) that a patient receives including the first vaccine dose, second vaccine dose, and booster doses)

      b) Name of vaccine(s)

      c) Timing in relation to BKEMV (i.e., the dates or duration that a patient receives BKEMV in relation to the meningococcal vaccine[s])

      d) ACIP compliance and antibacterial drug prophylaxis status

      e) Antibacterial drug prophylaxis regimen

      f) Timing (i.e., include the dates or duration that a patient receives BKEMV in relation to antibacterial drug prophylaxis)

      g) Clinical course:

         1) Outcome and causative meningococcal serogroup

         2) Source of the vaccine information when available. For information that is not available (listed as “unk” or “unknown”) the number and type (patient, prescriber, etc) of outreach attempts made to obtain the information for each case. Also, if the information is not available, a narrative is presented explaining why the information is unknown (“unk”) or unavailable for each reported case.

   vi. Whether or not he patient was administered any antibacterial drug prophylaxis was administered to the patient and if so:

a) The specific antibacterial drug, antibacterial drug regimen (dose/frequency/duration), and route(s) of administration

b) The timing of the course of the antibacterial drug prophylaxis in relation to BKEMV treatment

vii. Summary of the clinical course and the outcome; specifically report whether the patient:

a) Was admitted to an intensive care unit

b) Experienced any organ system failure, such as (but not limited to) requiring mechanical ventilation or medication (vasopressors) to support blood pressure

c) Died

viii. The length of time between onset of symptoms and when the patient presented for medical evaluation (if available)

ix. Causative meningococcal serogroups

x. Whether the **Patient Safety Card** was presented during the process of the patient seeking treatment

c. For each non-US case, the following information is provided:

i. Case report number

ii. Patient age and sex

iii. Indication for BKEMV treatment

iv. Meningococcal vaccination status if known

v. Outcome

vi. If associated with any clinical trials

10. Meningococcal Infections Rate (per year and cumulatively)

a. Among patients who received BKEMV in the US and worldwide,

i. The number of reported cases of meningococcal infections per 100 000 patient-years of postmarketing exposure to BKEMV; reporting rate, summarized cumulatively since the approval of BKEMV and also by year and relevant age subgroup (≤ 18 years, 19 - 55 years, and > 55 years).

Knowledge

11. Knowledge

    a. Stakeholder surveys for prescribing HCPs and patients (beginning with the 1-year REMS Assessment Report and provided for each reporting period annually thereafter)

        i. Assess HCP and patient awareness regarding:

            a) Vaccination of patients against meningococcal infections caused by Neisseria meningitidis serogroups A, C, W, Y, and B prior to starting therapy according to the most current ACIP recommendations for patients receiving a complement inhibitor, and antibacterial drug prophylaxis if needed.

            b) The early signs and symptoms of meningococcal infections.

            c) The need for immediate medical evaluation

Overall Assessment of REMS Effectiveness

12. The requirements for assessments of an approved REMS under Section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted.

Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

BLA 761333 REMS ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g.,
ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

BLA 761333 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR BLA 761333/ S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761333/ S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761333/ S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 761333/ S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR BLA 761333

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling.*

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, contact Caden Brennen, Safety Regulatory Project Manager, at 301-796-6591 or at Caden.Brennen@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Rosanna Setse, MD, MPH, PhD.
Deputy Director for Safety
Division of Nonmalignant Hematology
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURE:

- REMS

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/s/

ROSANNA W SETSE
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