BLA 761333

BLA APPROVAL

Amgen Inc.
Attention: Natalia Isaeva, RAC, PMP
Senior Manager, Global Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320

Dear Natalia Isaeva:

Please refer to your biologics license application (BLA) dated and received February 28, 2023, and your amendments, submitted under section 351(k) of the Public Health Service Act for Bkemv (eculizumab-aeeb) injection.

We acknowledge receipt of your major amendment dated February 27, 2024, which extended the goal date by three months. This BLA provides for Bkemv (eculizumab-aeeb) 300 mg/30 mL (10 mg/mL) injection, for intravenous use in a single-dose vial as interchangeable with US-Soliris 300 mg/30 mL (10 mg/mL) injection, for intravenous use in a single-dose vial.

LICENSING

We have approved your BLA for Bkemv (eculizumab-aeeb) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Bkemv under your existing Department of Health and Human Services U.S. License No. 1080. Bkemv is indicated for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis and for the treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture eculizumab-aeeb drug substance at (b) (4). The final formulated drug product will be manufactured and filled at (b) (4) The final formulated drug product will be labeled and packaged at (b) (4) (b) (4). You may label your product with the proprietary name, Bkemv, and market it in 300 mg/30 mL (10 mg/mL) single-dose vial, injection, for intravenous use.

DATING PERIOD

The dating period for Bkemv shall be 36 months from the date of manufacture when stored at 5 ± 3°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 (b) (4).

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.

We have approved the stability protocol in your license application for the purpose of extending the expiration dating period of your drug substance under 21 CFR 601.12.

FDA LOT RELEASE

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

FIRST INTERCHANGEABLE EXCLUSIVITY

Section 351(k)(6) of the PHS Act provides:

> The Secretary shall not make approval as an interchangeable biological product effective with respect to an application submitted under this subsection that relies on the same reference product for which a prior biological product has received a determination of interchangeability for any condition of use, until the earlier of—
>
> (A) 1 year after the first commercial marketing of the first interchangeable biosimilar biological product to be approved as interchangeable for that reference product;
>
> (B) 18 months after—
>
> (i) a final court decision on all patents in suit in an action instituted under subsection (l)(6) against the applicant that submitted the application forthe first approved interchangeable biosimilar biological product; or

(ii) the dismissal with or without prejudice of an action instituted under subsection (l)(6) against the applicant that submitted the application for the first approved interchangeable biosimilar biological product; or

(C)

(i) 42 months after approval of the first interchangeable biosimilar biological product if the applicant that submitted such application has been sued under subsection (l)(6) and such litigation is still ongoing within such 42-month period; or

(ii) 18 months after approval of the first interchangeable biosimilar biological product if the applicant that submitted such application has not been sued under subsection (l)(6).

For purposes of this paragraph, the term "final court decision" means a final decision of a court from which no appeal (other than a petition to the United States Supreme Court for a writ of certiorari) has been or can be taken and the term "first interchangeable biosimilar biological product" means any interchangeable biosimilar biological product that is approved on the first day on which such a product is approved as interchangeable with the reference product.

Bkemv (eculizumab-aeeb) injection, 300 mg/30 mL (10 mg/mL) for intravenous use is the first product relying on its reference product to receive a determination of interchangeability for any condition of use. Therefore, with this approval, this product qualifies as a first interchangeable biosimilar biological product for purposes of section 351(k)(6) of the PHS Act. The expiration date of any first interchangeable exclusivity has yet to be determined.

For each interchangeable biosimilar biological product approved by this letter, submit a general correspondence to this 351(k) BLA informing the Agency of the date of the first commercial marketing within 30 days of such date. Submit a duplicate copy of the correspondence via email to PurpleBook@fda.hhs.gov.

If applicable, please submit a general correspondence to this 351(k) BLA informing the Agency of the date of any final court decision (as defined in section 351(k)(6) of the PHS Act) on all patents in suit in any action implicating this BLA instituted under section 351(l)(6) of the PHS Act, or the date of dismissal with or without prejudice of any action implicating this BLA instituted under section 351(l)(6), within 30 days of such date or within 30 days of this approval if such date occurred prior to approval. If any action implicating this BLA instituted under section 351(l)(6) is still ongoing at the time of this approval, submit a general correspondence informing the Agency of this within 30 days of this approval. Submit a duplicate copy of the correspondence(s) via email to PurpleBook@fda.hhs.gov.

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.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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 and Medication Guide). 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.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

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 761333**." Approval of this submission by FDA is not required before the labeling is used.

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

[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.

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.

Because none of these criteria apply to your application, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Food Drug Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Bkemv to ensure the benefits of the drug outweigh the risk of serious meningococcal infections.

Your proposed REMS must also include the following:

Elements to assure safe use: Pursuant to 505-1(f)(1), we have determined that Bkemv can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risks of serious meningococcal infections listed in the labeling of the drug.

Your REMS includes the following elements to mitigate this risks:

- Healthcare providers have particular experience or training, or are specially certified
- Pharmacies or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions

Implementation System: The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above) that require: pharmacies or health care settings that dispense the drug be specially certified and the drug be dispensed to patients with documentation of safe use conditions.

Your proposed REMS, submitted on February 28, 2023, amended and appended to this letter, is approved.

The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Bkemv into interstate commerce.

The 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 or 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 the patient was administered any antibacterial drug prophylaxis 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) Patients are vaccinated 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 receive 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.

If the information provided in an assessment is insufficient to allow FDA to determine whether the REMS is meeting its goals or whether the REMS must be modified, FDA may require the submission of a new assessment plan that contains the metrics and/or methods necessary to make such a determination. Therefore, FDA strongly recommends obtaining FDA feedback on the details of your proposed assessment plan to ensure its success. To that end, we recommend that methodological approaches, study protocols, other analysis plans and assessment approaches used to assess a REMS program be submitted for FDA review as follows:

i. Submit your proposed audit plan and non-compliance plan for FDA review within 60 days of this letter.

ii. Submit your proposed protocol for the knowledge survey(s) for FDA review within 90 days of this letter.

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)**

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). 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, proposed 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 the 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 a REMS modification*, provide a rationale for why the REMS does not need to be modified.

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 REVISION 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, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

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

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 314.81(b)(3)(i)]. 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:

[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

If you have any questions, call Carleveva Thompson, Regulatory Project Manager, at 301-796-1403.

Sincerely,

{See appended electronic signature page}

Tanya Wroblewski, MD
Deputy Director
Division of Nonmalignant Hematology
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling
- REMS

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/

TANYA M WROBLEWSKI
05/28/2024 04:09:41 PM