BLA 761108/S-026
BLA 761108/S-031

SUPPLEMENT APPROVAL

Alexion Pharmaceuticals, Inc.
Attention: Perrine Geoffroy
Executive Director, Global Regulatory Affairs,
Development Strategy
121 Seaport Boulevard
Boston, MA 02210

Dear Perrine Geoffroy:

Please refer to your supplemental biologics license applications (sBLAs), dated and received August 5, 2022, for S-026, and December 12, 2022, for S-031, as well as your amendments, submitted under section 351(a) the Public Health Service Act for Ultomiris (ravulizumab-cwvz) injection.

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated August 5, 2022. Further, we acknowledge receipt of your amendment to S-26, which included proposed modifications to the approved Ultomiris risk evaluation and mitigation strategy (REMS), dated November 21, 2023, and constituted a complete response to our September 5, 2023, action letter.

Prior Approval sBLA S-26 provides for a new indication for the treatment of adult patients with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody positive and proposed modifications to the approved Ultomiris REMS. In addition, Prior Approval sBLA S-31 provides for proposed modifications to the approved Ultomiris REMS to form a combined REMS with Soliris. This supplement is in response, in part, to our May 16, 2023, REMS Modification Notification Letter.

APPROVAL & LABELING

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

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] that is identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

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*.[2]

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in these supplemental applications, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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 carton and container labeling submitted on March 15, 2024, 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*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761108/S-026**." 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 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

[1] 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 https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for sBLA S-026 because necessary studies are impossible or highly impracticable. This waiver is being granted because the number of children diagnosed with NMOSD is small.

Because none of these criteria apply to sBLA S-031, you are exempt from this requirement for sBLA S-031.

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 assess an unexpected serious risk of adverse maternal, fetal, and infant outcomes resulting from the use of Ultomiris (ravulizumab-cwvz) during pregnancy.

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:

4449-1 Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Ultomiris (ravulizumab-cwvz) during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.

The timetable you submitted on July 24, 2023, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/2023 (submitted)
Annual Interim Report Submissions:	10/2024
	10/2025
	10/2026
	10/2027

	10/2028
	10/2029
	10/2030
	10/2031
	10/2032
Study Completion:	10/2033
Final Report Submission:	07/2034

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 144187 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).**

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.

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, 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(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.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

[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.

The REMS for Ultomiris was originally approved on December 21, 2018, and the most recent REMS modification was approved on July 22, 2022. The REMS consists of elements to assure safe use and a timetable for submission of assessments of the REMS.

In order to ensure the benefits of Ultomiris outweigh its risks, we determined that you were required to make the REMS modifications outlined in our REMS Modification Notification letter dated May 16, 2023, and our Complete Response letter dated September 5, 2023. In addition, your proposed modifications to the REMS consist of the addition of the new indication for Ultomiris for the treatment of adult patients with NMOSD who are anti-aquaporin-4 (AQP4) antibody positive, updates to the materials to conform to the safety labeling changes approved on February 8, 2024, and changes to the REMS Document to:

- add an additional BLA number to include Soliris (BLA 125166)
- change the name of the REMS to the Ultomiris and Soliris REMS
- update the REMS Document and materials to include Soliris

Your proposed modified REMS, known as the Ultomiris and Soliris REMS, submitted on December 12, 2022, amended and appended to this letter, is approved. The modified REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. The modifications to the approved REMS must be fully implemented within 180 calendar days of the date of this letter.

The timetable for submission of assessments of the REMS must be revised to annually from the date of the approval of the Ultomiris and Soliris REMS.

Submit a REMS Assessment Report within 60 days of implementation of the approved REMS. For the Ultomiris REMS, the REMS Assessment Report will contain information from October 22, 2023, through one calendar day prior to implementation of the Ultomiris and Soliris REMS. Subsequent REMS Assessment Reports must be submitted annually from the date of the Ultomiris and Soliris REMS approval.

The REMS Assessment Plan must include, but is not limited to, the following:

For each metric, the two previous, current, and cumulative reporting periods (where applicable) will be provided unless otherwise noted.

Program Implementation and Operations

1. REMS implementation (for the first combined Ultomiris and Soliris REMS Assessment only)

a. Date of Ultomiris and Soliris REMS launch

b. Date when the Ultomiris and Soliris REMS Website became live and fully operational

c. Date when healthcare providers (HCPs), and healthcare settings and pharmacies were able to complete the REMS certification process

d. Date of first prescriber certification

e. Date of first healthcare setting and pharmacy certification

f. Date when the REMS Call Center was established and fully operational

g. Number and percentage of current active healthcare providers that certified in the new REMS

2. REMS Certification and Enrollment Statistics

a. Health Care Provider (HCP) Certification

i. The number of HCPs certified: total, newly certified, and active (prescribed Ultomiris or Soliris 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, Doctor of Pharmacy), 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 HCP 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 number and identity of certified dispensing healthcare settings and pharmacies: total, newly enrolled, and active (dispensed Ultomiris or Soliris at least once during the reporting period) stratified by type, (e.g., infusion center, specialty pharmacy) and by geographic region (as defined by US Census)

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

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 become certified

c. Patient statistics

i. The number and percent of new patients treated with Ultomiris or Soliris

ii. The number of patients treated with Ultomiris or Soliris stratified by sex, age, diagnosis, and geographic region (as defined by US Census)

iii. A comparison of the number of new patients treated with Ultomiris or Soliris to the number of patients treated

3. Ultomiris and Soliris Utilization Data

a. The number of Ultomiris and Soliris 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 Ultomiris and Soliris 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)

4. 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 prescribers, and healthcare settings and pharmacies,

actions taken to address noncompliance for each case, and what events led to suspension or de-certification 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:

1. The unique identification (ID) of the stakeholder(s) associated with the noncompliance event to enable tracking over time

2. The source of the noncompliance data

3. The results of root cause analysis

4. The action(s) taken in response to noncompliance

iii. The number and percentage of prescribers who prescribed Ultomiris or Soliris but were not certified as identified by the certified pharmacy

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

v. The number and percentage of healthcare settings and pharmacies who obtained Ultomiris or Soliris 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 de-certified, accompanied by a summary of reasons for de-certification

5. 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, and other entities that distribute Ultomiris or Soliris.

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, a designated Authorized Representative is certified, and certification 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 preventative measures that were developed from uncovering these noncompliance events.

   i. For stakeholders with observations noted within the audit report, provide the number that successfully completed a CAPA plan by the due date

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

6. 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 Call Center Report

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

      ii. A table summarizing the reasons for calls (e.g., enrollment 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

7. 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 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 Ultomiris or Soliris who report receiving meningococcal vaccination(s) out of the total number of patients who received Ultomiris or Soliris. 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 Ultomiris or Soliris who reported not receiving meningococcal vaccination(s) out of the total number of patients who received Ultomiris or Soliris.

d. Whether the patient received antibacterial drug prophylaxis, and timing of antibacterial drug prophylaxis in relation to the dosing of Ultomiris or Soliris (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. Pharmacy unable to get healthcare provider to respond to queries

f. The number and percentage of patients naïve to treatment with Ultomiris or Soliris 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 Ultomiris or Soliris 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

8. Summary of cases of meningococcal infections in patients receiving Ultomiris or Soliris

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

      i. In the most recent Periodic Safety Update Report (PSUR) submitted to the Ultomiris BLA or Soliris BLA with reference to the 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, the following information is provided:

      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 Ultomiris or Soliris 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 Ultomiris or Soliris (i.e., the dates or duration that a patient receives Ultomiris or Soliris 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 Ultomiris or Soliris 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 Ultomiris or Soliris treatment

vii. Summary of clinical course and the outcome; specifically, 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 Ultomiris or Soliris treatment

iv. Meningococcal vaccination status if known

v. Outcome

vi. If associated with any clinical trials

9. Meningococcal Infections Rate (per year and cumulatively)

a. Among patients who received Ultomiris or Soliris in the US and worldwide:

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

Knowledge

10. Knowledge

a. Stakeholder surveys for prescribing HCPs and patients (beginning with the first combined Ultomiris and Soliris REMS Assessment Report and annually thereafter)

i. Assess healthcare provider (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

11. 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.

Additionally, we recommend that you submit your proposed full audit plan and non-compliance plan for FDA review within 60 days of this letter, and that you submit your proposed protocols for the healthcare provider and patient knowledge surveys for FDA review within 90 days of this letter. Prominently identify the submissions containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission: **"REQUEST FOR REMS ASSESSMENT METHODOLOGY PROTOCOL REVIEW/ AUDIT PLAN AND COMPLIANCE PLAN" or "REQUEST FOR REMS ASSESSMENT METHODOLOGY PROTOCOL REVIEW/ SURVEY METHODOLOGIES",** respectively, in bold capital letters, at the top of your cover letter and at the top of the first page of the main submission document.

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. 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 761108 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 761108 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR BLA 761108/ S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761108/ S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761108/ 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 761108/ 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 761108

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.

REQUESTED PHARMACOVIGILANCE

We request that you perform postmarketing surveillance and enhanced pharmacovigilance for serious adverse events related to infection, including opportunistic infections. Report all confirmed or possible cases to the BLA in an expedited fashion and include comprehensive summaries and analyses of these events as part of your required postmarketing safety reports (e.g., periodic safety update reports [PSURs]). Include analyses of the events by indication for use of Ultomiris, age, and sex. 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 and the causality, including extent of exposure to Ultomiris and most recent exposure to Ultomiris, concomitant therapies, treatment given for the event, and outcome.

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.*[4]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in supplement 26, including any new safety-related information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4).

[4] For the most recent version of a guidance, check the FDA guidance web page athttps://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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 Bethany Shelbourne, Regulatory Project Manager, via email at bethany.shelbourne@fda.hhs.gov or by phone at (301) 796-9265.

Sincerely,

{See appended electronic signature page}

Paul R. Lee, MD, PhD
Director
Division of Neurology 2
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- 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/

PAUL R LEE
03/22/2024 02:40:04 PM