BLA 761108/S-040
BLA 125166/S-450 **SUPPLEMENT APPROVAL**

Alexion Pharmaceuticals, Inc.
Attention: Gary Perry
Director, Regulatory Science & Execution
121 Seaport Blvd, Boston, MA 02210

Dear Gary Perry:

Please refer to your supplemental biologics license applications (sBLA) received April 29, 2025, and your amendments, submitted under section 351(a) of the Public Health Service Act for BLA 761108 Ultomiris (ravulizumab-cwvz) injection and BLA 125166 Soliris (eculizumab) injection.

These Changes Being Effected supplemental new drug applications proposed modifications to the approved Ultomiris and Soliris risk evaluation and mitigation strategy (REMS).

We have completed our review of these supplemental applications, as amended. They are approved effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Soliris was originally approved on June 4, 2010, and the REMS for Ultomiris was originally approved on December 21, 2018. The two drugs are subject to the same REMS known as the Ultomiris and Soliris REMS. The most recent REMS modification was approved on February 28, 2025. 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 removal of the Alexion REMS landing webpage from the REMS Document, and changes to the REMS Website (UltSolREMS.com).

Your proposed modified REMS, submitted on April 29, 2025, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on March 22, 2024.

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 re-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:

         a) The unique identification (ID) of the stakeholder(s) associated with the noncompliance event 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 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 and pharmacies).

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 and the healthcare setting and pharmacy is certified. If the Authorized Representative has changed, include the number of the newly Authorized Representatives and verification of each 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** (www.UltSolREMS.com)

      i. The number of visits and unique visits to the **REMS Website** (www.UltSolREMS.com)

      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 certified HCPs and patients (beginning with the first combined ULTOMIRIS and SOLIRIS REMS Assessment Report and annually thereafter)

i. Assess certified 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 you submit your updated audit plan, non-compliance plan, and proposed protocols for the healthcare provider and patient knowledge surveys for FDA review within 30 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 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:

BLAs 761108/125166 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:

BLAs 761108/125166 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR BLA 761108/ S-000; BLA 125166/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761108/ S-000; BLA 125166/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761108/ S-000; BLA 125166/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; BLA 125166/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 BLAs 761108; 125166

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

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/

ROSANNA W SETSE
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