BLA 761108/S-23

SUPPLEMENT APPROVAL

Alexion Pharmaceuticals, Inc.
Attention: Lindsay Durniak MS, RAC
Senior Specialist, GRA, Development Strategy
121 Seaport Boulevard
Boston, MA 02210

Dear Ms. Durniak:

Please refer to your supplemental biologics license application (sBLA), dated and received October 27, 2021, and your amendments submitted under section 351(a) of the Public Health Service Act for Ultomiris (ravulizumab-cwvz) injection.

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated October 27, 2021.

This Prior Approval supplemental biologics license application provides for the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody-positive and proposed modifications to the approved Ultomiris REMS.

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

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.

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.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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 this supplemental application, 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

We acknowledge your October 27, 2021, submission containing final printed carton and container labeling.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement from birth to 12 years because necessary studies are impossible or highly impracticable. This is because the product does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used in a substantial number of pediatric patients in this age group.

We are deferring submission of your pediatric study for ages 12 to 17 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

[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.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(4)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

4252-1 Conduct a multicenter, open-label, single arm study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of ravulizumab in pediatric patients ages 12 through 17 with AChR antibody-positive myasthenia gravis. This study will use comparable C5 level inhibition from adults to pediatrics to establish partial extrapolation using comparative PK/PD between pediatric patients ages 12 through 17 and adults.

Draft Protocol Submission: 06/2022
Final Protocol Submission: 09/2022
Study Completion: 07/2028
Final Report Submission: 01/2029

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 the protocol(s) to your IND 140115, with a cross-reference letter to this BLA. Reports of this required pediatric postmarketing study must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient identify the unexpected serious risk of adverse maternal, fetal, and infant outcomes resulting from exposure to Ultomiris during pregnancy.

[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.

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 study:

4252-2	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 April 12, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2022
Final Protocol Submission:	10/2023
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.[4]

Submit the protocols to your IND 140115, with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing 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**

[4] 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.

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

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70 . We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Ultomiris was originally approved on December 21, 2018, and the most recent REMS modification was approved on November 23, 2021. The REMS consists of elements to assure safe use and a timetable for submission of assessments of the REMS.

Your proposed modification to the REMS consists of a revised Prescriber Safety Brochure to include the indication for generalized myasthenia gravis. In addition, changes to all educational REMS materials were made to align with labeling.

Your proposed modified REMS, submitted on February 4, 2022, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on December 21, 2018.

There are no changes to the REMS assessment plan described in our December 2, 2021, REMS Assessment Acknowledgment/REMS Assessment Plan Revision Letter. The REMS assessment plan must include, but is not limited to, the following items:

A. Program Implementation and Operations:

1. Healthcare Provider Certification (per reporting period and cumulatively)
    a. Numbers certified: total, newly certified, and active (ordered Ultomiris at least once during the reporting period), stratified by credentials, medical specialty, and geographic region (as defined by US Census)
    b. Method of certification

2. Patient statistics (per reporting period and cumulatively)
    a. The number and percentage of new patients treated with Ultomiris and enrolled in the OneSource program
    b. Demographics of patients treated with Ultomiris (gender, age, diagnosis, geographic region)
    c. A comparison of the number of new patients treated with Ultomiris to the number of patients treated and enrolled in the OneSource program

3. REMS Compliance (per reporting period and cumulatively)
    a. Provide a summary of non-compliance identified, including, but not limited to:
        i. Provide a copy of the non-compliance plan, including the criteria for non-compliance for prescribers, actions taken to address non-compliance for each case, and what events led to suspension or decertification from the REMS.
    b. Number and percentage of prescribers who prescribed Ultomiris but were not certified
    c. Specific reasons that prescribers were not certified at the time of prescribing
    d. Actions taken to ensure that no prescriber who was not certified was allowed to prescribe Ultomiris and that all prescribers of Ultomiris were certified
    e. Root causes analyses of instances where non-certified prescribers were distributed Ultomiris (especially those cases where more than one distribution was made to a non-certified prescriber)
    f. Actions taken to ensure that all prescribers are certified

4. REMS Website (per reporting period and cumulatively)
    a. Number of visits and unique visits to the REMS website
    b. Number of REMS materials downloaded or printed for each material

5. Coordinating Center Report (per reporting period)
    a. Number of contacts by stakeholder type (patient/caregiver, healthcare provider, etc.
    b. A table summarizing the reasons for calls (e.g., enrollment question) by stakeholder type

c. If the summary 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
d. A summary report of corrective actions resulting from issues identified

6. Materials Distribution Metrics (per reporting period)
    a. Number of materials packets sent as part of prescriber reminder education and returned as undeliverable, by date and method

B. Safe Use Behaviors

7. Safe Use Behaviors (per reporting period and cumulatively)
    a. Provide the methods utilized to determine whether or not patient meningococcal vaccinations were in accordance with the current ACIP recommendations. Include- vaccine serotype, dosing, and timing of the vaccinations, when the information is provided.
    b. Provide data on the number and percentage of new patients treated with Ultomiris who report receiving meningococcal vaccination(s) out of the total number of patients who received Ultomiris.
        i. Of those that reported receiving meningococcal vaccinations, provide the number and percentage of patients who:
            1. Received vaccinations in accordance with current ACIP recommendations for persons who have complement deficiency.
            2. Did not receive vaccinations in accordance with current ACIP recommendations for persons who have complement deficiency.
            3. Did not recall whether the vaccination they received was in accordance with ACIP recommendations.
    c. Provide data on the number and percentage of new patients treated with Ultomiris who reported not receiving meningococcal vaccination(s) out of the total number of patients who received Ultomiris.
            1. Of those, the number and percentage who recalled being offered the meningococcal vaccination.
    d. Provide data on the number and percentage of new patients treated with Ultomiris who declined to provide meningococcal vaccination(s) status out of the total number of patients who received Ultomiris.
            1. Of those, the number and percentage who recalled being offered the meningococcal vaccination.
    e. Provide data on the number and percentage of new patients treated with Ultomiris who did not recall their meningococcal vaccination(s) status out of the total number of patients who received Ultomiris.
            1. Of those, the number and percentage who recalled being offered the meningococcal vaccination.

C. Health Outcomes and/or Surrogates of Health Outcomes

8. Summary of cases of meningococcal infections in patients receiving Ultomiris (per reporting period and cumulatively)
    a. For US cases, summarize cases as follows:
        i. In the most recent PSUR submitted to the Ultomiris BLA with a link to that PSUR identified
        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 report and date of report to FDA
        iii. Age, race, and gender
        iv. Indication for Ultomiris treatment
        v. Meningococcal vaccination status, to include the specific vaccines; the dates they were administered; your conclusions as to whether the vaccinations were received in accordance with the ACIP guidelines; and references to the specific versions of the ACIP guidelines that were in effect at the time the infections occurred
        vi. Whether the patient was administered any prophylactic antibiotics and if so:
            1. The specific antibiotics, antibiotic regimen (dose/frequency), and routes of administration
            2. The duration of the antibiotic treatment
            3. The timing of the course of the antibiotics in relation to Ultomiris treatment
        vii. Summary of clinical course and the outcome; specifically report whether the patient:
            1. Was admitted to an intensive care unit
            2. Experienced any organ system failure, such as (but not limited to) requiring mechanical ventilation or medication (vasopressors) to support blood pressure
            3. Died
        viii. Causative meningococcal serotype
        ix. Whether the Patient Safety Card was presented during the process of the patient seeking treatment
    c. For each non-US case, provide the following information:
        i. Case report number
        ii. Patient age and gender
        iii. Indication for Ultomiris 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 in the US and worldwide, the number of reported cases of meningococcal infection per 100,000 patient-years of post-marketing exposure to Ultomiris; reporting rate will be summarized cumulatively since the approval of Ultomiris and also by year and relevant age subgroup (≤18 years, 19-55 years, and >55 years).

D. Knowledge (per reporting period):

10. Starting with the 12-month reporting period, an assessment of healthcare provider (HCPs) understanding regarding:
    a. the increased risk of meningococcal infections with Ultomiris
    b. the early signs of invasive meningococcal infections
    c. the need for immediate medical evaluation of signs and symptoms consistent with possible meningococcal infections

11. Starting with the 12-month reporting period, an assessment of patient understanding regarding:
    a. the increased risk of meningococcal infections with Ultomiris
    b. the early signs of invasive meningococcal infections
    c. the need for immediate medical evaluation of signs and symptoms consistent with possible meningococcal infections

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

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

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

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

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

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

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

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

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

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

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

BLA ###### 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 section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

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 ###### REMS ASSESSMENT

or

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

or

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

or

NEW SUPPLEMENT BLA ######/ 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 ######/ 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 ######

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

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the 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 SPL format using the FDA automated drug registration and listing system (eLIST).

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

REQUESTED PHARMACOVIGILANCE

We request that you perform postmarketing surveillance for serious events related to infection including opportunistic infection and for adverse cerebrovascular events including transient ischemic attack (TIA) and stroke. Include analyses of individual events as well as comprehensive summaries and analyses of these events, including incidence, quarterly 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 or the causality, including extent of exposure to Ultomiris and most recent exposure to Ultomiris, concomitant therapies, treatment given for the event, and outcome. For cerebrovascular events include a comparison of incidence to an appropriate background rate.

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.*[5]

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.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

[5] For the most recent version of a guidance, check the FDA guidance web page athttps://www.fda.gov/media/128163/download.
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] 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 Justine Kankam, Regulatory Project Manager, at 1-(301)-837-7650 or via email at NanaYaa.Kankam@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Teresa Buracchio, MD
Director
Division of Neurology 1
Office of Neuroscience
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- 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/

TERESA J BURACCHIO
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