CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761108Orig1s000

Trade Name:	Ultomiris Injection, 300 mg / 30mL (10 mg / mL)
Generic or Established:	Ravulizumab-cwvz
Sponsor:	Alexion Pharmaceuticals Inc.
Approval Date:	December 21, 2018
Indication:	For the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761108

BLA APPROVAL

Alexion Pharmaceuticals Inc.
Attention: Mike Page
Executive Director, Global Regulatory Affairs
100 College Street
New Haven, CT 06510

Dear Mr. Page:

Please refer to your Biologics License Application (BLA) dated June 18, 2018, received June 18, 2018, and your amendments, submitted under section 351(a) of the Public Health Service Act for ULTOMIRIS™ (ravulizumab-cwvz) injection, 300 mg/30 mL (10 mg/mL).

LICENSING

We have approved your BLA for ULTOMIRIS (ravulizumab-cwvz) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, ULTOMIRIS under your existing Department of Health and Human Services U.S. License No. 1743. ULTOMIRIS is indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture ravulizumab-cwvz drug substance at (b) (4) The final formulated drug product will be manufactured and filled at Alexion (b) (4), and labeled and packaged at Alexion (b) (4). You may label your product with the proprietary name, ULTOMIRIS, and market it in 300 mg/30 mL vials.

DATING PERIOD

The dating period for ULTOMIRIS shall be 24 months from the date of manufacture when stored at 2-8 °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) from the date of manufacture when stored at (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 protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of ULTOMIRIS 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 ULTOMIRIS, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL AND 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 text.

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. 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 titled "*SPL Standard for Content of Labeling Technical Qs and As*" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

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 carton and container labeling submitted on November 15, 2018, 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 titled *Providing Regulatory Submissions in Electronic Format — Certain Human*

Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5). For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761108**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for ULTOMIRIS was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected for a biologic of this class in the intended population.

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3557-1 Submit the final clinical study reports and datasets for randomized controlled trials of ULTOMIRIS in patients with paroxysmal nocturnal hemoglobinuria (ALXN1210-PNH-301 and ALXN1210-PNH-302) to include the extension period of up to 2 years of follow-up.

The timetable you submitted on December 10, 2018, states that you will conduct this study according to the following schedule:

Interim Report Submission: 06/2019
Final Report Submission: 09/2020

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3557-2 Implement a two-tier Reference material system with (b) (4) storage condition for primary reference material.

The timetable you submitted on December 12, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2019

3557-3 Explore alternative assay formats for the Hemolytic assay in order to reduce the method variability.

The timetable you submitted on December 12, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2019

3557-4 Qualify the (b) (4) sample for the bioburden method using samples from three (b) (4) lots. Provide the qualification data.

The timetable you submitted on December 12, 2018, states that you will conduct this study according to the following schedule:

Final Report Submission: 07/2019

Submit clinical protocols to your IND 128367 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

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 ULTOMIRIS™ (ravulizumab-cwvz) to ensure the benefits of the drug outweigh the risk of meningococcal infection.

Your proposed REMS must also include the following:

Elements to assure safe use: Pursuant to 505-1(f)(1), we have also determined that ULTOMIRIS™ (ravulizumab-cwvz) can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risk of meningococcal infection. Your REMS includes the following elements to mitigate this risk:

- Healthcare providers have particular experience or training, or are specially certified

Your proposed REMS, submitted on June 18, 2018, amended and appended to this letter, is approved.

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

Your REMS must be fully operational before you introduce ULTOMIRIS™ (ravulizumab-cwvz) into interstate commerce.

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

1. Prescriber Enrollment (per reporting period and cumulatively):
   a. Number enrolled: total and newly enrolled
      Number of non-enrolled prescribers with specific reasons why prescribers did not enroll
   b. Actions taken to ensure that all prescribers of ULTOMIRIS are enrolled and non-enrolled prescribers are not allowed to prescribe ULTOMIRIS
   c. Root causes analyses of instances where non-enrolled prescribers were distributed ULTOMIRIS

2. Patient statistics (per reporting period and cumulatively):
   a. The number of new patients treated with ULTOMIRIS
   b. Demographics of patients treated with ULTOMIRIS (gender, age, race, diagnosis)
   c. Number of new patients treated with ULTOMIRIS receiving meningococcal vaccinations according to current Advisory Committee on Immunization Practices (ACIP) recommendations for persons who have complement deficiency. Information regarding the vaccines administered is to include vaccine serotype, dosing, and timing of the vaccinations.

3. Summary of cases of U.S. meningococcal infections (per reporting period and cumulatively):
   a. For each 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, including whether vaccinations were administered in compliance with the most current Advisory Committee on Immunization Practices (ACIP) recommendations with regards to vaccine product, dosage, and timing
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 the clinical course and the outcome
viii. causative meningococcal serogroup
ix. whether the Patient Safety Card was presented during the process of the patient seeking treatment
x. Whether the patient had received the Patient Safety Brochure

b. Provide a link to the most recent Periodic Safety Update Report (PSUR)

4. Rate (# cases/100,000 patient-years) of meningococcal infections (per reporting period and cumulatively) for U.S. cases, worldwide cases, and relevant age subgroups (ages 0-18 years, 18-55 years, and >55 years).

5. Starting with the 12-month reporting period, an assessment of prescribing healthcare professionals (HCPs) understanding regarding:
    - the increased risk of meningococcal infections with ULTOMIRIS
    - the early signs of invasive meningococcal infections
    - the need for immediate medical evaluation of signs and symptoms consistent with possible meningococcal infections

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

7. 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). 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.

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 761108 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY

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

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

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 REVISION 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, 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

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.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (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 for licensed biological products (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:

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Natasha Kormanik, Regulatory Project Manager, at (240) 402-4227.

Sincerely,

{See appended electronic signature page}

Amy McKee, MD
Acting Associate Director
Office of Hematology and Oncology Products
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/

AMY E MCKEE
12/21/2018