

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761108Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761108
PDUFA Goal Date	February 18, 2019
OSE RCM #	2018-1308 and 2018-1310
Reviewer Name(s)	Mei-Yean Chen, Pharm.D. Kate Oswell, M.A., Health Communication Analyst
Team Leader	Elizabeth Everhart, MSN, RN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	December 19, 2018
Subject	Review of REMS
Established Name	Ravulizumab
Trade Name	Ultomiris
Name of Applicant	Alexion Pharmaceuticals Inc.
Therapeutic Class	Complement Inhibitor
Formulation(s)	300 mg vial via Intravenous Infusion
Dosing Regimen	Dose varies by body weight and loading versus maintaining

1 Introduction

This review by the Division of Risk Management (DRISK) to evaluate Alexion's proposed REMS for Ultomiris (ravulizumab). Alexion submitted a Biologic License Application (BLA) 761108 for ravulizumab with the proposed indication for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH). This product is very similar to the same sponsor's product, Soliris (eculizumab), except ravulizumab requires less frequent dosing; every 8 weeks versus every 2 weeks for eculizumab. The most serious risk associated with C5 complement inhibition is increased susceptibility to infections caused by *Neisseria meningitidis*. This inherent risk with complement inhibition has been well characterized with the use of eculizumab. Due to its identical binding epitope on C5 and mechanism of action of near complete terminal complement inhibition, ravulizumab carries the same risk of serious meningococcal infection as eculizumab. Life-threatening and fatal meningococcal infections, such as meningitis, have occurred in patients treated with eculizumab. Eculizumab is approved with a REMS with elements to assure safe use (ETASU) to mitigate the risk of meningococcal infection.

Because this product carries the same risk of serious meningococcal infection, the sponsor has proposed a risk evaluation and mitigation strategy (REMS) for ravulizumab which is identical to the requirements in the Soliris (eculizumab) REMS Program. The sponsor's proposed REMS consists of ETASU (prescriber training) and a timetable for submission of assessments.

DRISK and Division of Hematology Products (DHP) agree that a REMS with ETASU consisting of education of prescribers and patients is necessary to ensure that the benefits of ravulizumab outweigh the risks of meningococcal infections.

2 Background

2.1 PRODUCT INFORMATION

Ravulizumab is a complement Inhibitor proposed for treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH). Ravulizumab, a derivative of eculizumab, is a humanized monoclonal antibody (mAb) that binds to terminal complement protein C5, a part of the complement system, thereby blocking C5 cleavage into pro-inflammatory components and preventing the complement-mediated destruction of red blood cells (RBCs) as seen in patients with PNH. Eculizumab, the current standard of care for PNH, is the only approved treatment for patients with PNH. Compared to eculizumab, which requires dosing every 2 weeks, ravulizumab extends the dosing interval to 8 weeks. Ravulizumab differs from eculizumab at 4 amino acid substitutions in the heavy chain. These substitutions are intended to enable an extended dosing interval by increasing the circulating half-life.

As described in our 10/05/2018 REMS review, DRISK and DHP determined that ravulizumab is required to have a REMS to ensure that the benefits of the drug outweigh the increased risk of meningococcal infections. Alexion initially submitted a REMS on 06/18/2018, and provided amendments on 10/19/2018, 11/7/2018, 12/12/2018, and 12/18/2018.

2.2 REGULATORY HISTORY

Following is a summary of the regulatory history for BLA 761108 relevant to this review:

- 06/18/2018: BLA 761108 submission for treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) along with a rare pediatric disease priority review voucher.
- 09/04/2018: The REMS Oversight Committee (ROC)^a agreed with the review team proposal that the REMS for ravulizumab should be identical to the REMS for eculizumab with the exception the timetable for submission of assessments should be at 6 months, 12 months, and annually thereafter.^b
- 10/05/2018: The Agency sent comments to the sponsor on REMS document, supporting document, materials, and assessment plan. Details are provided in the October 4, 2018 review by DRISK.^c
- 10/19/2018: The sponsor amended their submission. They accepted all of the Agency's comments/edits with the exception of:
 1. REMS document, Section III, 1., REMS Requirements item 8 for HCPs, the sponsor is proposing to delete (b) (4) d for serious meningococcal infections"
 2. REMS document: Section III, 2., To support the REMS program operations Alexion Pharmaceuticals, Inc. is proposing (b) (4)
 3. REMS supporting document: Under the Key Risk Message, the sponsor proposed to delete fatal in "life threatening and fatal meningococcal infections have occurred in patients treated with Ultomiris.
- 11/01/2018: The Agency sent additional comments to the sponsor which included the following: .
 - *REMS document: Section III, 2., We do not agree with your current proposal (b) (4) As this is a new REMS, prescribers should use one of the other four enrollment options (i.e., fax, mail, email or online).*
- 11/07/2018: The sponsor submitted amended REMS document, materials, and supporting document.
- 11/08/2018 and 11/09/2018: The Agency sent comments to the sponsor regarding the 11/7/18 submission. The comments are summarized below:

^a As per the 21st Century review process, all REMS with elements to assure safe use (ETASU) are discussed at the REMS Oversight Committee (ROC) which consists of senior level management from the Offices of New Drugs, Surveillance and Epidemiology, and Regulatory Policy.

^b Toigo, T: REMS Oversight Committee (ROC) by email, 09/04/2018

^c Chen, Mei-Yean. Division of Risk Management Evaluation of the Need for a REMS. October 4, 2018. DARRTS reference ID 433049

Prescriber Safety Brochure:

In your comments to us, you agreed to make the change below. However, the materials do not show this change in the redline or clean versions. Include this change with your next submission.

- Page two, first bullet under the heading “Risk of Serious Meningococcal Infections,” revise content to reflect the Prescribing Information: “Life-threatening meningococcal infections/sepsis have occurred in patients treated with Ultomiris”
- The Prescriber Brochure contains a reference to a footnote that was removed from the content. Remove the number reference on the third bullet under “Immunization.”

REMS Website:

In the submission from 11/07/18, both website files are outdated, as the agreed upon changes made in your submission on 10/19/18 are not included. Please include the most recent agreed upon version of the website with your REMS submission.

REMS supporting document:

- On page 4, item 3, the timetable for submission of REMS assessments should be corrected to **6 months, 1 year, and annually thereafter beginning DD MMM YYYY.**
- On page 4, item 5, in the heading, delete the word (b) (4) that appears before Risk Evaluation and Mitigation Strategy for Ultomiris (Ravulizumab)
- 12/11/2018: The agency sent a comment stating that in order for DRISK to continue our review of the REMS, please send a complete REMS and all materials in final format with the language “Consider discontinuation of ULTOMIRIS in patients who are undergoing treatment for serious meningococcal infection.”
- 12/12/2018: The sponsor submitted the REMS, REMS supporting document, and REMS materials with all the required changes except in the enrollment form of REMS material “consider discontinuation of Ultomiris in patients who are undergoing treatment for serious meningococcal infection”.
- 12/17/2018: An IR was sent to the sponsor for correction of the enrollment form and for a final submission of the REMS and appended materials.
- 12/18/2018: The sponsor submitted final REMS with all the required changes.

3 Materials reviewed

3.1 SUBMISSIONS AND IRs

The following submissions were reviewed from BLA 761108 for the proposed Ultomiris REMS:

- 06/18/2018: Proposed REMS, eCTD Sequence #001
- 10/05/2018: REMS IR to the sponsor and REMS review in DARRTS
- 10/19/2018: REMS Correspondence, eCTD Sequence #0016
- 11/01/2018: REMS IR to the sponsor
- 11/07/2018: The sponsor response to the IR, eCTD Sequence #0023

- 11/08/2018 and 11/09/2018: REMS IR to the sponsor
- 12/12/2018: The sponsor response to the IR, eCTD Sequence #0039
- 12/17/2018: REMS IR to the sponsor.
- 12/18/2018: The sponsor response to the IR, eCTD Sequence #0042

3.2 OTHER MATERIALS INFORMING OUR REVIEW

- Draft labeling submitted 07/03/2018, 10/25/2018, 12/5/2018, and 12/17/2018
- Dr. Nguyen, Robert. Office of Prescription Drug Promotion, in DARRTS October 29, 2018

4 Therapeutic Context/Treatment Options and Benefit Assessment

The therapeutic context, including a description of the medical condition and current treatment options, is provided in the October 4, 2018 review, available in DARRTS.

The efficacy and safety of ravulizumab in patients with PNH was assessed in two populations:

- Study 1 (NCT 02946463): a complement-inhibitor-naïve population of patients with active hemolysis to assess the efficacy.
- Study 2 (NCT 03056040): a population of patients stable on eculizumab therapy that allowed the assessment of the maintenance of efficacy and safety in a population switching to ravulizumab^d.

In the two clinical trials, all primary endpoints in both studies achieved non-inferiority of ravulizumab compared to eculizumab in overall population.^e In Study 1, both coprimary endpoints, avoidance of transfusion per protocol-specified guidelines and LDH normalization from day 29 to day 183, met the primary objective and showed ravulizumab was statistically significant for noninferiority compared to eculizumab. In study two the primary outcome measure was hemolysis as measured by LDH percent change from baseline to day 183.

5 Proposed REMS

This section describes the REMS submitted by the sponsor on December 18, 2018. See appendix for the REMS and appended REMS materials:

5.1 REMS GOALS

The goals of the REMS are:

- To mitigate the occurrence and morbidity associated with meningococcal infections
- To educate healthcare providers (HCPs) and patients regarding:
 - the increased risk of meningococcal infections with Ultomiris

^d Chen, Mei-Yean. Division of Risk Management Evaluation of the Needs for a REMS. October 4, 2018. DARRTS reference ID 433049

^e Setse, R. and Dwyer, K. Clinical and statistical Midcycle presentation. 09/24/2018.

- o the early signs of invasive meningococcal infections, and
- o the need for immediate medical evaluation of signs and symptoms consistent with possible meningococcal infections

Reviewer comment: This is acceptable.

5.2 REMS DOCUMENT

The sponsor has made all changes required by the Agency.

- **Reviewer comment: This is acceptable.**

5.3 REMS MATERIALS

The sponsor has made all changes required by the Agency.

Reviewer comment: This is acceptable.

5.4 REMS SUPPORTING DOCUMENT

The sponsor has made all changes required by the Agency.

Reviewer comment: This is acceptable.

5.5 TIMETABLE FOR SUBMISSION OF ASSESSMENTS

Alexion must submit REMS assessments 6 months, 12 months, and annually thereafter from the date of the initial approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Alexion Pharmaceuticals, Inc. must submit each assessment so that it will be received by the FDA on or before the due date.

Reviewer comment: This is acceptable.

5.6 REMS ASSESSMENT PLAN

The REMS assessment plan includes, 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.

Reviewer Comment: *This is acceptable.*

6 Comments on the REMS from Office of Prescription Drugs (OPDP)

DRISK consulted OPDP to review the REMS and appended materials. The OPDP reviewer (Robert Nguyen, PharmD) provided the following language from the draft Prescribing Information: “Carry [the Patient Safety Card] with you at all times during treatment and for several months after your last Ultomiris dose.” OPDP notes that on the Patient Safety Card, Patient Brochure and in other information for patients on the REMS Website, patients are instructed to carry the card at all times. OPDP recommends aligning the language with the Medication Guide.

DRISK did not accept OPDP’s comments because the recommended language does not align with the REMS Document. As a part of the requirements in the REMS document, the patients must keep the Patient Safety Card on them at all times. The timeframe of this key message is easier to convey to patients and easier for patients to understand and remember. DRISK provides OPDP’s comments for OND’s consideration.

7 Discussion

Soliris and ravulizumab are both complement inhibitors that specifically bind to the complement protein C5, thereby inhibiting formation and activation of the terminal complement complex. This inhibition blocks the function of the complement system in both normal and abnormal conditions. The complement system is an important component of immunity to some bacterial infections. Ravulizumab is associated with an increased risk of meningococcal infection because it inhibits terminal complement, making patients more susceptible to infection with encapsulated organisms including *Neisseria meningitides*.

The REMS submitted by the sponsor on December 18, 2018 provides the same level of safety as the eculizumab REMS because it educates prescribers and patients about the need for vaccination per ACIP guidelines, educates prescribers about the need to monitor patients for signs of meningococcal infection, and educates both prescribers and patients that vaccination reduces, but does not eliminate the risk of developing meningococcal infection. Prescribers are trained about the risk of meningococcal infection and the need to counsel patients, and patients are provided a safety brochure, as well as a wallet card that they are counseled to carry with them at all times. The purpose of the wallet card is twofold: 1) it serves as a reminder for patients about the symptoms of meningococcal infection and 2) the card allows for the patient to alert a healthcare provider who had not prescribed ravulizumab that the patient has received ravulizumab and may be at risk of meningococcal infection. The wallet card is to be presented to any healthcare providers the patient sees, and in particular, healthcare providers at an emergency care facility.

If ravulizumab is approved, in addition to the REMS, the serious risk of meningococcal infections will be communicated in a boxed warning, Dosage and Administration, Contraindications, and Warnings and Precautions sections of the product label.

DHP and DRISK agree that, should ravulizumab be approved, an ETASU REMS comprised of prescriber training is necessary to ensure that the benefits of ravulizumab outweigh its risks of meningococcal infection. The sponsor has made all required changes to the REMS document, REMS materials, REMS supporting document, and REMS assessment plan.

8 Conclusion & Recommendations

A REMS consisting of ETASU is necessary to ensure that the benefits outweigh the risks of serious meningococcal infection. The sponsor has made all the required changes to the REMS; DRISK recommends approval of the ravulizumab REMS.

9 Appendices: REMS document and appended REMS materials.

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/s/

MEI-YEAN T CHEN
12/19/2018

ELIZABETH E EVERHART
12/19/2018
I concur.

CYNTHIA L LACIVITA
12/19/2018
concur

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

**U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Hematology and Oncology Products
Division of Hematology Products**

NDA/BLA #s:	BLA 761108
Products:	ULTOMIRIS (ravulizumab-cwvz) injection
APPLICANT:	Alexion Pharmaceuticals
FROM:	Barry W. Miller, Deputy Director, Safety (acting)
DATE:	December 17, 2018

Section 505-1 of the Federal Food, Drug, and 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 [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for Ultomiris to ensure that the benefits of the drug outweigh the risks of meningococcal infection. In reaching this determination, we considered the following (as described in the DRISK review dated 10/4/2018, M-Y Chen, C LaCivita):

- A. The estimated number of patients in the United States with paroxysmal nocturnal hemoglobinuria (PNH) is 15.9 per million. This estimate is based on Hill A, et al. Blood. 2006; 108(11)L 290a.
- B. PNH is a progressive, destructive, and life-threatening disease in which uncontrolled complement activation leads to systemic complications, principally through intravascular hemolysis and thrombophilia.
- C. The efficacy and safety of ravulizumab in patients with PNH was demonstrated in 2 populations: 1) complement-inhibitor-naïve population of patients with active hemolysis, and 2) patients stable on eculizumab therapy that allowed the assessment of the maintenance of efficacy and safety in a population switching to ravulizumab.

- D. Patient's benefiting from treatment may be continued on ravulizumab every 8 weeks, indefinitely.
- E. Ravulizumab is a humanized monoclonal antibody that binds to component 5 (C5) and blocks its activation by complement pathway convertases. The most serious risk associated with C5 complement inhibition is increased susceptibility to infections caused by *Neisseria meningitidis*. This inherent risk with complement inhibition has been well characterized with the use of eculizumab. Use of eculizumab is associated with >1000-fold increase in incidence of meningococcal disease. Due to its identical binding epitope on C5 and mechanism of action of near complete terminal complement inhibition, ravulizumab carries the same risk of serious meningococcal infection as eculizumab.
- F. Ultomiris is a biologic product, not a drug classifiable as a new molecular entity.

The REMS will consist of elements to assure safe use to mitigate the risk of meningococcal infection, including education of healthcare providers and patients, and a timetable for submission of assessments of the REMS.

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/s/

BARRY W MILLER
12/18/2018

Internal Consults

****Pre-decisional Agency Information****

Please Note: The following review is for DRISK only and should not be used to provide comments to the sponsor.

To: Kate Oswell, Health Communications Analyst,
Division of Risk Management (DRISK),
Office of Surveillance and Epidemiology (OSE)

From: Robert Nguyen, PharmD, Regulatory Review Officer, OPDP

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP
Wana Manitpisitkul, Safety Regulatory Project Manager, OSE
Elizabeth Everhart, Team Leader, DRISK
Joyce Weaver, Risk Management Analyst, DRISK
Doris Auth, Associate Director, DRISK
Carole Broadnax, OPDP
Michael Wade, OPDP
CDER-OPDP-RPM

Date: October 29, 2018

Re: BLA 761108
ULTOMIRIS™ (ravulizumab) injection, for intravenous use
Comments on draft Risk Evaluation and Mitigation Strategies (REMS)
Materials (Submission date: August 22, 2018)

Materials Reviewed

OPDP has reviewed the following proposed REMS materials for Ultomiris:

- Healthcare Provider (HCP) REMS Materials:
 - o Ultomiris Prescriber Safety Brochure
 - o Ultomiris REMS HCP Enrollment Form
- Direct-to-Consumer (Patient) REMS Materials:
 - o Ultomiris Patient Safety Brochure
 - o Ultomiris Patient Safety Card
- Ultomiris REMS Website

The version of the draft REMS materials used in this review were sent from DRISK (Kate Oswell) via email on October 22, 2018. The draft REMS materials are attached to the end of this review memorandum.

OPDP offers the following comments on these draft REMS materials for Ultomiris.

General Comment

Please remind Alexion Pharmaceuticals, Inc. that REMS materials are not appropriate for use in a promotional manner.

REMS Materials

OPDP does not object to including the following materials in the REMS program (please see Specific Comments below):

- o Ultomiris Prescriber Safety Brochure
- o Ultomiris REMS HCP Enrollment Form
- o Ultomiris Patient Safety Brochure
- o Ultomiris Patient Safety Card
- o Ultomiris REMS Website

Specific Comments

OPDP considers the following statements promotional in tone and recommends revising or deleting them from the REMS piece:

- Ultomiris Prescriber Safety Brochure
 - o Page two of the Ultomiris Prescriber Safety Brochure includes the following statement under the header **“Risk of Serious Meningococcal Infections”**: (b) (4)
[REDACTED]

- **Risk**

This claim minimizes REMS risks of the drug by omitting the following material information from the Boxed Warning of the draft Ultomiris Prescribing Information (PI) (emphasis added):

“Life-threatening meningococcal infections/sepsis have occurred in patients treated with Ultomiris”

By omitting this material information, the statement may minimize the severity of the REMS risk. We recommend revising the Prescriber Safety Brochure to include this material information.

- o Page two of the Ultomiris Prescriber Safety Brochure includes the following statement under the header “**Immunization**”:
“Do not initiate Ultomiris therapy in patients with unresolved serious *Neisseria meningitidis* infection...”

- **Risk**

This claim is inconsistent with the draft Ultomiris PI and suggests that Ultomiris therapy should not be initiated only in patients with unresolved serious *Neisseria meningitidis* infection. However, Section 4, Contraindications, states:

“Ultomiris is contraindicated in patients with unresolved *Neisseria meningitidis* infection.”

We recommend revising this statement to be consistent with Section 4 of the draft Ultomiris PI.

- o Page two of the Ultomiris Prescriber Safety Brochure includes the following statement under the header “**Monitoring Patients**”:

(b) (4)

 for serious meningococcal infections.”

- **Risk**

While we acknowledge that this product is contraindicated in patients with unresolved *Neisseria Meningitidis* infection, we note that the draft PI does not include information regarding discontinuing Ultomiris in patients currently undergoing treatment who develop a serious meningococcal infection. We defer to DHP and DRISK as to whether this is an appropriate directive for patients who develop a serious meningococcal infection during treatment with Ultomiris and if this section should be revised to be consistent with the draft PI.

- o Page four of the Ultomiris Prescriber Safety Brochure includes the following statement under the header “**Patient Safety Card**”:
“**Tell your patients to carry this card at all times,**” (emphasis original).

- **Risk**

- This claim omits material information from the draft Ultomiris Medication Guide (MG) necessary for the safe use of Ultomiris. Specifically, the draft MG states (emphasis added):

- “Carry [the Patient Safety Card] with you at all times during treatment and for ^{(b) (4)} months after your last ULTOMIRIS dose.”

- We recommend revising this statement to include this material information from the draft Ultomiris MG.

- Ultomiris Patient Safety Brochure

- o The Ultomiris Patient Safety Brochure includes the following header
“**Getting Your Vaccine**” (emphasis original).

- **Risk**

- In order to improve consumer comprehension of the meningococcal vaccination requirements associated with the REMS risk, as described in this section, we recommend revising the header to state, “**Getting your Meningococcal Vaccines**” (bolded emphasis original, underline emphasis added).

- o The Ultomiris Patient Safety Brochure includes the following statement under the header “**Patient Safety Card**”:
“Carry this card at all times.”

- **Risk**

- This claim omits material information from the draft Ultomiris Medication Guide (MG) necessary for the safe use of Ultomiris. Specifically, the draft MG states (emphasis added):

- “Carry [the Patient Safety Card] with you at all times during treatment and for ^{(b) (4)} months after your last ULTOMIRIS dose.”

- We recommend revising this statement to include this material information from the draft Ultomiris MG.

- Ultomiris REMS Website

- o Page two of the Ultomiris REMS Website includes a section titled “**Patient Counseling.**” The second bullet in this section states:

- “Remind patients to carry the Patient Safety Card with them at all times.”
- o The fifth bullet in this section includes the statement:
 - “...Even if a patient stops using Ultomiris, they should keep their Ultomiris Patient Safety Card with them.”
- **Risk**

In order to improve communication of the directive to patients regarding the Patient Safety Card as necessary for the safe use of Ultomiris, we recommend revising the “Patient Counseling” section of the website to include the material information contained in these bullets in direct conjunction with each other.

We have no additional comments on these proposed REMS materials at this time.

Thank you for your consult.

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/s/

ROBERT L NGUYEN
10/29/2018

Division of Risk Management (DRISK)
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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Ultomiris (ravulizumab) is necessary to ensure the benefits outweigh its risks. Alexion Pharmaceuticals, Inc. submitted a Biologic Licensing Application (BLA) 761108 for ravulizumab with the proposed indication for treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH). Ravulizumab is a humanized monoclonal antibody that binds to component 5 (C5) and blocks its activation by complement pathway convertases. This product is very similar to the same applicant's product, Soliris (eculizumab), except that it requires less frequent dosing; every 8 weeks versus every 2 weeks for eculizumab. The most serious risk associated with C5 complement inhibition is increased susceptibility to infections caused by *Neisseria meningitidis*. This inherent risk with complement inhibition has been well characterized with the use of eculizumab. Due to its identical binding epitope on C5 and mechanism of action of near complete terminal complement inhibition, ravulizumab carries the same risk of serious meningococcal infection as eculizumab. Life-threatening and fatal meningococcal infections, such as meningitis, have occurred in patients treated with eculizumab. Eculizumab is approved with a REMS with elements to assure safe use (ETASU) to mitigate the risk of meningococcal infection.

The applicant has proposed a REMS for ravulizumab which is identical to the requirements in the eculizumab REMS. The applicant's proposed REMS consists of ETASU (prescriber training), an implementation system, and a timetable for submission of assessments.

The other serious risks associated with ravulizumab use are increased susceptibility to infections, PNH manifestation after ravulizumab discontinuation, importance of thrombosis prevention and management, and infusion reactions. If approved, these risks will be communicated in the warnings and precautions section of the labeling.

DRISK and Division of Hematology Products (DHP) agree that a REMS is needed to ensure the benefits of ravulizumab outweigh its risks. Based on the magnitude and severity of the meningococcal infections, we agree that requiring a REMS with ETASU consisting of education of prescribers and patients is necessary to ensure that the benefits of ravulizumab outweigh the risk of meningococcal infections without causing undue burden to stakeholders is necessary to ensure that the benefits of ravulizumab outweigh the risk of meningococcal infections.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)^a Ultomiris (ravulizumab) is necessary to ensure the benefits outweigh its risks. Alexion Pharmaceuticals, Inc. (Alexion) submitted a Biologic Licensing Application (BLA) 761108 for ravulizumab with the proposed indication for treatment of adult

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

patients with paroxysmal nocturnal hemoglobinuria (PNH). This application is under review in the Division of Hematology Products (DHP).

2 Background

2.1 PRODUCT INFORMATION

Ravulizumab is a complement Inhibitor proposed for treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH). Ravulizumab, a derivative of eculizumab, is a humanized monoclonal antibody (mAb) that binds to terminal complement protein C5, a part of the complement system, thereby blocking C5 cleavage into pro-inflammatory components and preventing the complement-mediated destruction of red blood cells (RBCs) as seen in patients with PNH. Eculizumab, the current standard of care for PNH, is the first and only approved treatment for patients with PNH. Compared to eculizumab, which requires dosing every 2 weeks, ravulizumab extends the dosing interval to 8 weeks. Ravulizumab differs from eculizumab at 4 amino acid substitutions in the heavy chain. These substitutions are intended to enable an extended dosing interval by increasing the circulating half-life. The recommended dosing regimen for adult patients with PNH consists of a loading dose followed 2 weeks later by maintenance dosing every 8 weeks to be given by intravenous (IV) infusion. The doses to be administered are based on the patient's body weight, as shown in table 1. Treatment with ravulizumab is usually for a patient's life time.^b Ravulizumab is not currently approved in any jurisdiction. The sponsor submitted marketing application in Europe in July 2018 and anticipates submission in Japan in October 2018.

Table 1: Ultomiris weight-based dosing regimen

Body weight (kg)	Loading dose (mg)	Maintenance dose (mg)
≥ 40 to <60	2400	3000
≥ 60 to <100	2700	3300
≥ 100	3000	3600

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761108 relevant to this review:

- January 4, 2017: orphan drug designation granted under IND 128367.
- June 12, 2018: pre-BLA meeting decided this application will be under the OHOP pilot review. The applicant uses its pediatric voucher, thus this application will have a priority review.
- June 18, 2018: BLA 761108 submission for treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) along with a rare pediatric disease priority review voucher.

^b Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- September 4, 2018: By email, the REMS Oversight Committee (ROC)^c agreed with the review team proposal that the REMS for ravulizumab should be identical to the REMS for eculizumab with the exception the timetable for submission of assessments should be at 6 months, 12 months, and annually thereafter.¹

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

PNH is an ultra-rare (prevalence 15.9/million)^{2, d} progressive, destructive, and life-threatening disease in which uncontrolled complement activation leads to systemic complications, principally through intravascular hemolysis and thrombophilia. Complement mediated hemolysis is the hallmark of PNH disease. An acquired mutation of the phosphatidylinositol glycan class A (PIG-A) gene caused PNH. The mutation of the PIG-A gene leads to a lack of CD55 and CD59. CD55 and CD59 are naturally occurring terminal complement inhibitor proteins on cell surfaces. The continuous activation of the alternative complement pathway and chronic intravascular hemolysis are the results of absence of these complement inhibitor proteins and leads to inflammation, platelet activation, and hemolysis. As a result of hemolysis, free hemoglobin is released, nitric oxide is consumed, smooth muscle cell contracts persistently, and increase risk of severe thromboembolism. At any time, exacerbations of the disease state may occur, either spontaneously or due to increased complement activation following infections, trauma, or physical exertion. Lactate dehydrogenase (LDH) is the best direct measure of complement-mediated intravascular hemolysis.

Patients with PNH are at risk of substantial morbidity and mortality.^e The median age at diagnosis is early 30s. Before the availability of eculizumab, 35% of patients with PNH die within 5 years of diagnosis,³ with a median survival of 10 years after diagnosis. In PNH, all cells that arise from the defective stem cell also carry the mutated PIG-A gene. These cells are deficient in a class of proteins called glycosylphosphatidylinositol (GPI) anchored proteins. Certain GPI-anchored proteins protect red blood cells from destruction while some are involved in blood clotting. Thrombotic events (TEs) are the leading cause of death in patients with PNH. Compared with the general population, patients with PNH have a 62-fold higher risk of a TE⁴ and a six-fold greater risk of chronic kidney disease (CKD).⁵ Patients with PNH have a decreased quality of life, which may include the inability to support themselves and social isolation due to debilitating fatigue, chronic pain, poor physical function, shortness of breath,

^c As per the 21st Century review process, all REMS with elements to assure safe use (ETASU) are discussed at the REMS Oversight Committee (ROC) which consists of senior level management from the Offices of New Drugs, Surveillance and Epidemiology, and Regulatory Policy.

^d Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

^e Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

abdominal pain, erectile dysfunction, frequent therapeutic interventions and hospitalization due to a need for anticoagulation, and the need for blood transfusions and/or dialysis.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The only approved drug for PNH is eculizumab, which was approved in 2007 in the United States (US) and subsequently in many countries globally.

Eculizumab is a humanized monoclonal antibody (mAb) that targets C5 of the terminal complement cascade, inhibiting its cleavage during complement activation into complement component 5a and complement component 5b. Eculizumab is effective in reducing hemolysis, improving quality of life and reducing the risk of TEs in patients with PNH. However, some patients treated with eculizumab have suboptimal C5 blockade, leaving them at risk of breakthrough hemolysis and potentially life-threatening TEs.⁶ Also eculizumab therapy is to be given every 2 weeks which causes missed work or school. Another burden to patients and their family is they need to schedule their life events and travel carefully to accommodate this biweekly treatment.

Because of its mechanism of action of complement inhibition, a REMS for eculizumab was originally approved in June 2010 to address the risk of meningococcal infections. The most recently approved REMS consists of elements to assure safe use (ETASU) and a timetable for submission of assessments of the REMS.

4 Benefit Assessment

The efficacy and safety of ravulizumab in patients with PNH was assessed in 2 populations:^{f7}

- Study 1 (NCT 02946463): a complement-inhibitor-naïve population of patients with active hemolysis to assess the efficacy.
- Study 2 (NCT 03056040): a population of patients stable on eculizumab therapy that allowed the assessment of the maintenance of efficacy and safety in a population switching to ravulizumab.

Study 1:

Study 1 enrolled patients who were complement-inhibitor naïve. This was a 26-week, multicenter, open-label, active-controlled, phase 3 study conducted in 25 countries. A total of 246 patients were enrolled, 125 patients in the ravulizumab group and 121 patients in the eculizumab group. Of the 246, 244 patients completed the primary evaluation period; 2 patients in the eculizumab group prematurely discontinued study drug. Patients enrolled had active hemolysis as evidenced by the laboratory parameter of Lactate Dehydrogenase (LDH) $\geq 1.5 \times$ Upper Limits of Normal (ULN) plus the presence of a

^f Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

clinical sign or symptom of active intravascular hemolysis: fatigue, hemoglobinuria, abdominal pain, shortness of breath, anemia, major adverse vascular event, dysphagia, or erectile dysfunction.

The co-primary endpoints were transfusion avoidance and hemolysis as directly measured by normalization of LDH levels. Transfusion avoidance was considered as achieved only by the patients who did not receive a transfusion and did not meet the protocol specified guidelines for transfusion from baseline up to day 183. Key secondary endpoints included the percent change from baseline in LDH levels, change in quality of life, the proportion of patients with breakthrough hemolysis and proportion of patients with stabilized hemoglobin.

In Study 1, both coprimary endpoints, avoidance of transfusion per protocol-specified guidelines and LDH normalization from day 29 to day 183, met the primary objective and showed ravulizumab was statistically significant for noninferiority compared to eculizumab. Ravulizumab also achieved statistically significant noninferiority compared to eculizumab for all 4 key secondary endpoints. Both coprimary endpoints and all key secondary endpoints favored ravulizumab.

Study 2:

Study 2 enrolled patients who were treated with eculizumab. This was a 26-week, multicenter, open-label, active-controlled phase 3 study conducted in 195 patients with PNH who were clinically stable after having been treated with eculizumab for at least the past 6 months. PNH medical history was similar between ravulizumab and eculizumab treatment groups. The 12-month transfusion history was similar between two groups and more than 87% of patients in both groups had not received a transfusion within 12 months of study entry. All patients presented with controlled hemolysis at baseline; consistent with a population under continuous treatment with eculizumab.

The primary outcome measure was hemolysis as measured by LDH percent change from baseline. Secondary outcome measures included the proportion of patients with breakthrough hemolysis, quality-of-life, transfusion avoidance, and proportion of patients with stabilized hemoglobin.

In Study 2, the primary endpoint, percent change in LDH from baseline to day 183, met the primary objective and showed ravulizumab was statistically significant for noninferiority compared to eculizumab. Ravulizumab also achieved statistically significant noninferiority compared to eculizumab for all 4 key secondary endpoints. Both primary endpoints and all 4 key secondary endpoints favored ravulizumab.

5 Risk Assessment & Safe-Use Conditions

Across the clinical studies in patients with PNH, a total of 261 patients who received ravulizumab were included in the safety database. No deaths were reported in the pooled ravulizumab group up to the date cutoff.

5.1 SERIOUS MENINGOCOCCAL INFECTIONS^{g,8}

Ravulizumab is a humanized monoclonal antibody that binds to component 5 (C5) and blocks its activation by complement pathway convertases. The most serious risk associated with C5 complement inhibition is increased susceptibility to infections caused by *Neisseria meningitidis*. This inherent risk with complement inhibition has been well characterized with the use of eculizumab. Use of eculizumab is associated with >1000 fold increase in incidence of meningococcal disease. Due to its identical binding epitope on C5 and mechanism of action of near complete terminal complement inhibition, ravulizumab carries the same risk of serious meningococcal infection as eculizumab. Three meningococcal infections were reported in the ravulizumab clinical development program⁹: 2 in the phase 2 study (meningococcal infection on day 57 and meningococcal sepsis on day 222), and 1 in the phase 1b study (meningococcal infection on day 615). All 3 patients recovered while remaining on ravulizumab without treatment interruption.

To reduce this risk of infection, all patients must be vaccinated against meningococcal infections prior to initiating ravulizumab. Patients who initiate ravulizumab therapy less than 2 weeks after receiving a meningococcal vaccine must receive prophylactic antibiotics until 2 weeks after vaccination. Patients must be vaccinated or revaccinated according to most current Advisory Committee on Immunization Practices recommendations for patients with complement deficiencies. Patients should be monitored for early signs of meningococcal infection and sepsis and informed of these signs and symptoms and advised to seek medical care immediately.

To mitigate the risk of meningococcal infection with ravulizumab therapy, the sponsor proposed a REMS program, ravulizumab is only available through this restricted program that prescribers must enroll in the program. Prescribers must counsel patients about the risk of meningococcal infection, provide the patients with the REMS educational materials, and ensure patients are vaccinated with meningococcal vaccines.

5.2 INCREASED SUSCEPTIBILITY TO INFECTIONS

Due to its mechanism of action of complement inhibition, patients receiving ravulizumab may have increased susceptibility to infections. If approved, the product label will advise in the warning and precautions section that patients are informed of this potential risk via a patient brochure.

5.3 DISEASE MANIFESTATIONS AFTER RAVULIZUMAB DISCONTINUATION

If patients with PNH discontinue treatment with ravulizumab, they may experience worsening signs and symptoms of PNH. If ravulizumab is approved, the label will advise in the warning and precautions section that prescribers closely monitor them for signs and symptoms of hemolysis to detect hemolysis and other reactions.

^g Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

5.4 THROMBOSIS PREVENTION AND MANAGEMENT

Similar to Soliris, the label will advise that anticoagulation management should not be altered because of the risk of the development of thrombosis.

5.5 INFUSION REACTIONS

In clinical trials, some patients with PNH experienced infusion reactions which were described as mild in severity and transient. None of the infusion reactions required discontinuation of ravulizumab. If ravulizumab is approved, this risk will be communicated in the warning and precautions section of the label.

6 Expected Postmarket Use

Ravulizumab is likely to be used both inpatient and outpatient healthcare setting. Outpatient setting includes infusion center or home healthcare.

Ravulizumab is likely prescribed by hematologists/oncologists who are specialized in the management of patients with PNH.

7 Risk Management Activities Proposed by the Applicant

REVIEW OF APPLICANT'S PROPOSED REMS¹⁰

The applicant proposed a REMS includes requirements that are identical to the Soliris (eculizumab), REMS, with the exception that the REMS assessment is to be done every 6 months for the first year, then once a year. Ravulizumab has the same mechanism of action as eculizumab, as a complement inhibitor, except that it requires less frequent dosing, every 8 weeks versus every 2 weeks for eculizumab.

7.1.1. REMS Goals

The applicant proposed the following:

The goals of the REMS are:

- To mitigate the occurrence and morbidity associated with meningococcal infections.
- To educate Healthcare Providers (HCPs) and patients regarding:
 - The increased risk of meningococcal infections with Ultomiris
 - The early signs of invasive meningococcal infections, and
 - The need for immediate medical evaluation of signs and symptoms consistent with possible meningococcal infections.

Reviewer's Comments: *This is acceptable.*

7.1.2 REMS Requirements

The applicant proposes a REMS requirements comprising the following:

Alexion Pharmaceuticals, Inc. must ensure that HCPs comply with following requirement:

a) **HCPs who prescribe** (Ultomiris) must to become certified to prescribe by:

1. Review the drug's prescribing information
2. Review the following: (Ultomiris) patient safety card, (b) (4) prescriber safety brochure, and patient safety brochure.
3. (b) (4)
4. (b) (4)
5. Enroll in the REMS by completing the prescriber enrollment form and submitting it to the REMS program (b) (4)

b) Before treatment initiation (b) (4)

6. Assess the patient's meningococcal vaccine status and immunize patients (b) (4)
7. Provide the patient with a prescription for a two-week course of antibiotics prophylaxis if Ultomiris must be started (b) (4)
8. Counsel the patient (b) (4) using the patient safety card and patients safety brochure. Provide a copy of the materials to the patients. (b) (4)

c) During treatment: (b) (4)

9. Assess the patient for early signs of meningococcal infection and evaluate immediately if infectin is suspected.

10. Revaccinate patients according to the Advisory Committee on Immunization Practices recommendations.

d) At all times, (b) (4)

11. (b) (4) report cases of meningococcal infection, including the patient's clinical outcomes, (b) (4)

(b) (4)
(b) (4)
(b) (4)
(b) (4)
Alexion Pharmaceuticals, Inc. (b) (4)
(b) (4)
(b) (4)

Alexion must ensure **patients** who are prescribed (Ultomiris) comply the following requirement:

a) Before treatment initiation

1. (b) (4) patient safety card; patient safety brochure)
2. (b) (4) meningococcal vaccines (b) (4)
(b) (4) take antibiotics for two weeks (b) (4)
(b) (4)
3. Receive counseling from the prescriber (b) (4)
(b) (4)
(b) (4)

b) (b) (4)
(b) (4)

c) At all times

6. (b) (4) patient safety card.
7. Inform the prescriber or get emergency medical care right away (b) (4) if you (b) (4) headache with nausea or vomiting; headache and a fever; headache with a stiff neck or stiff back; fever; fever and a rash; confusion; muscle aches with flu-like symptoms; eyes sensitive to light.
8. (b) (4)

Reviewer's Comments: The REMS that was submitted by the applicant has been edited as attached in the appendix of this review.

7.1.3 REMS Materials & Key Risk Messages

Key Risk Messages

The applicant did not propose any Key Risk Messages

Reviewer's Comments: FDA recommends the following Key Risk Messages:

Key risk messages for HCPs:

1. Ultomiris is associated with the risk of meningococcal infection
 - a. Life threatening and fatal meningococcal infections have occurred in patients treated with Ultomiris.
2. Immunize all patient with meningococcal vaccines at least 2 weeks prior to administering the first dose of Ultomiris.
 - a. Vaccination reduces, but does not eliminate the risk of meningococcal infections.
 - b. Provide a patient with a prescription for a two-week course of antibiotic prophylaxis if Ultomiris must be started right away.
3. Monitor patients for early signs of meningococcal infections and evaluate immediate if infection is suspected.
4. Patients should be counseled using the Patient Safety Brochure and Patient Safety Card.
 - a. Instruct patient to carry the Patient Safety Card at all times and show the card to any healthcare professional that provides treatment.
 - b. Tell patients to seek immediate medical attention if they develop any of the following symptoms: headache with nausea or vomiting, headache with a stiff neck or stiff back, fever and rash, muscle aches with flu-like symptoms, headache and a fever, confusion, eyes sensitive to light.

Key risk messages for patients/caregivers:

1. Ultomiris increases your chance of getting serious and life threatening meningococcal infections.
2. Meningococcal infections may quickly become life threatening and cause death if not recognized and treated early.
3. Call your doctor or get emergency medical care right away if you get any signs or symptoms of a meningococcal infection.
 - a. Signs and symptoms may include: headache with nausea or vomiting, headache with a stiff neck or stiff back, fever and rash, muscle aches with flu-like symptoms, headache and a fever, confusion, eyes sensitive to light.
4. Carry the Ultomiris Patient Safety Card at all times. Show the card to any healthcare professional that treats you.

The applicant proposes REMS Materials comprising the following:

Enrollment Forms:

Prescriber: 1. Prescriber Enrollment Form

Reviewer's Comments: *This is acceptable*

Training and Educational Materials:

Prescriber: 2. Prescriber Safety Brochure

3. (b) (4)

Patient: 4. Patient Safety Card

5. Patient Safe Brochure

Reviewer's Comments: *Remove #3*

(b) (4)

And re-number the rest accordingly.

(b) (4)

Other Materials:

REMS Program Website ([www. Ultomiris.com](http://www.Ultomiris.com))

Reviewer's Comments: *Phone numbers used by the Ultomiris REMS may not link to information that is promotional in tone. The REMS specific website should not be the sole source of REMS materials. Include a prominent REMS-specific link to the Ultomiris REMS website on all product websites for consumers and healthcare providers. Under patient counseling heading: Remove the first bullet,*

(b) (4)

Replace with the following two bullets:

- o Counsel patients using both the patient safety brochure and patient safety card. Provide these materials to your patients.*
- o Remind patients to carry the patient safety card with them at all times.*

The drug name Ultomiris is misspelled in a few places on the REMS webpage. Correct as needed.

7.1.4 REMS Assessment Plan

The Applicant proposes the following REMS Assessment Plan:

Program outline

1. REMS Goals: same as above
2. RMES Compliance Plan: Alexion will establish a process to ensure compliance and follow-up for any non-complaint prescribers.
3. Timetable for Submission of Assessments: (b) (4)
(b) (4)
4. Information Needed for Assessment
 - a) Prescriber Enrollment
 - Numbers enrolled: total and newly enrolled (b) (4)
 - Number who are prescribing Ultomiris who are not enrolled
 - Specific reasons that prescribers did not enroll
 - Actions taken to ensure that no prescriber who is not enrolled is allowed to prescribe Ultomiris and that all prescribers of Ultomiris are enrolled
 - Root cause analyses of instances where non-enrolled prescribers were distributed Ultomiris (b) (4)
(b) (4)
 - Actions taken to ensure that all prescribers are enrolled
 - b) Patient statistics
 - The number of new patients treated with Ultomiris (b) (4)
(b) (4)
 - Demographics of patients treated with Ultomiris (gender, age group, diagnosis) (b) (4)
(b) (4)
 - Number of new patients treated with Ultomiris receiving meningococcal vaccination according to current ACIP recommendations for persons who have complement deficiency (b) (4) Information regarding the vaccines administered is to include vaccine serotype, dosing, and timing of the vaccinations.
 - c) Summary of cases of US (b) (4) meningococcal infections
(b) (4)
 - (b) (4) reporting period (b) (4)
(b) (4)

- Cumulative (b) (4)

- For each case, provide the following information:
 - Medwatch or other case report number
 - Date of report and date of report to FDA
 - Age and gender
 - Indication for Ultomiris treatment
 - Meningococcal vaccination status, including whether vaccinations are administered in compliance with the most current ACIP recommendations with regards to vaccine product, dosage, and timing
 - Whether the patient was administered any prophylactic antibiotics and if so:
 - *The specific antibiotics, antibiotics regimen (dose/frequency), and routes of administration
 - *The duration of the antibiotics treatment
 - *The timing of the course of the antibiotics in relations to Ultomiris treatment
 - Summary of clinical course and the outcome
 - Causative meningococcal sero (b) (4)
 - Whether the Patient Safety (b) (4) Card was presented during the process of the patient seeking treatment.

- d) Rate (number of cases/100,000 patient-years) of invasive meningococcal infections (b) (4) reporting period; (b) (4) for US cases, worldwide cases, and relevant age subgroups (ages 0 to (b) (4) years, 18 to 55 years, and >55 years) (b) (4)

Reviewer's Comments: We have revised the REMS assessment plan that was submitted. Please see the revised assessment appended for details, including required Knowledge, Attitudes, and Behavior (KAB) surveys for prescribers and patients (assessments of prescriber and patient understanding). The timetable for submission of assessments has been revised to require REMS assessments to be submitted at 6 months, 1 year, and annually thereafter from the time of approval.

7.1.5 REMS Supporting Document

Reviewer's Comments: The REMS supporting document must align with final FDA approved REMS document and labeling.

7.2 OTHER PROPOSED RISK MANAGEMENT ACTIVITIES

The applicant did not propose other risk management activities.

8 Discussion of Need for a REMS

DHP and DRISK agree that, should ravulizumab be approved, an ETASU REMS will be needed to ensure that the benefits of ravulizumab outweigh its risks. Ravulizumab is a humanized monoclonal antibody that binds to C5 and acts as a complement inhibitor which dosing every 8 weeks versus every 2 weeks for eculizumab. The administrations of eculizumab and ravulizumab increase a patient's susceptibility to serious meningococcal infections (septicemia and/or meningitis). Life-threatening and fatal meningococcal infections have occurred in patients treated with eculizumab and it is approved with an ETASU REMS to mitigate the risk of meningococcal infection.

Due to the same mechanism of action, ravulizumab also increases the patient's susceptibility to meningococcal infections. The applicant has proposed a REMS for ravulizumab which included requirements which are identical to the eculizumab REMS. Prescribers must counsel patients about the risk of meningococcal infection, provide the patients with the REMS educational materials, and ensure patients are vaccinated with meningococcal vaccines prior to starting ravulizumab.

If ravulizumab, is approved, in addition to the REMS, the serious risk of meningococcal infections will be communicated in a boxed warning, Dosage and Administration, Contraindications, and Warnings and Precautions sections of the product label.

The REMS for ravulizumab was discussed by REMS Oversight Committee (ROC) by email in September 2018. The ROC agreed that the ravulizumab REMS should include the same requirements as the eculizumab REMS.

The other serious risks associated with ravulizumab use are increased susceptibility to infections, PNH manifestation after ravulizumab discontinuation, thrombosis prevention and management, and infusion reactions. If approved, these risks will be communicated in the warnings and precautions section of the labeling.

9 Conclusion & Recommendations

The risk of meningococcal infections associated with ravulizumab is serious and it is necessary for prescribers and patients to understand these risks and the importance of monitoring for them. Based on the magnitude and severity of the meningococcal infections, we agree that a REMS with ETASU consisting of educating prescribers and patients regarding the risks is necessary to ensure that the

benefits of ravulizumab outweigh the risk of meningococcal infections . We have provided edited versions of the REMS document, assessment plan, and comments on the REMS materials for the applicant.

10 Comments for the Applicant

Comments for the applicant:

- To facilitate review of your submission, REMS-related materials in Microsoft Word, in track-change and clean versions.
- Phone numbers used by the Ultomiris REMS may not link to information that is promotional in tone.
- The REMS specific website should not be the sole source of REMS materials. Include a prominent REMS-specific link to the Ultomiris REMS website on all product websites for consumers and healthcare providers.
- We note that the label is still under negotiations with the Agency. All REMS communication materials must align with the final FDA approved label.
- Include all formatting when submitting REMS materials in your next submission, including any logos, coloring, shading, or other design features.

Key Risk Messages: Incorporate the following Key Risk Messages into your REMS supporting document:

Key risk messages for HCPs:

1. Ultomiris is associated with the risk of meningococcal infection
 - a. Life threatening and fatal meningococcal infections have occurred in patients treated with Ultomiris.
2. Immunize all patient with meningococcal vaccines at least 2 weeks prior to administering the first dose of Ultomiris.
 - a. Vaccination reduces, but does not eliminate the risk of meningococcal infections.
 - b. Provide a patient with a prescription for a two-week course of antibiotic prophylaxis if Ultomiris must be started right away.
3. Monitor patients for early signs of meningococcal infections and evaluate immediate if infection is suspected.
4. Patients should be counseled using the Patient Safety Brochure and Patient Safety Card.
 - a. Instruct patient to carry the Patient Safety Card at all times and show the card to any healthcare professional that provides treatment.
 - b. Tell patients to seek immediate medical attention if they develop any of the following symptoms: headache with nausea or vomiting, headache with a stiff neck or stiff back, fever and rash, muscle aches with flu-like symptoms, headache and a fever, confusion, eyes sensitive to light

Key risk messages for patients/caregivers:

1. Ultomiris increases your chance of getting serious and life threatening meningococcal infections.

2. Meningococcal infections may quickly become life threatening and cause death if not recognized and treated early.
3. Call your doctor or get emergency medical care right away if you get any signs or symptoms of a meningococcal infection.
 - a. Signs and symptoms may include: headache with nausea or vomiting, headache with a stiff neck or stiff back, fever and rash, muscle aches with flu-like symptoms, headache and a fever, confusion, eyes sensitive to light
4. Carry the Ultomiris Patient Safety Card at all times. Show the card to any healthcare professional that treats you.

REMS Webpage:

- Under Patient Counseling heading: Remove the first bullet, (b) (4)
 [REDACTED] Replace with the following two bullets:
 - o Counsel patients using both the Patient Safety Brochure and Patient Safety Card. Provide these materials to your patients.
 - o Remind patients to carry the Patient Safety Card with them at all times.
 - The drug name Ultomiris is misspelled in a few places on the REMS webpage. Correct as needed.
- We request a response to these comments by October 19, 2018.

REMS Document :

The REMS that was submitted by the applicant has been edited and is attached.

REMS Assessment plan

The REMS assessment plan has been updated and is attached. The revised assessment plan should be included in the REMS Supporting Document. The timetable for submission of REMS assessments has been revised to require the submission of REMS assessments at 6 months, 1 year, and annually thereafter from the date of approval.

11 Appendices: REMS document and assessment plan

12 REFERENCES

- 1 Toigo, T; REMS Oversight Committee (ROC) by email, September 4, 2018.
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- 5 Hillman P, et al. Long-term effect of the complement inhibitor eculizumab on kidney function in patients with PNH. Am J Hematol. 2010 Aug; 85(8): 553-9

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- 6 Setse, R and Wroblewski, T clinical reviewers of Division of Hematologic Products, mid-cycle presentation of rabulizumab, September 24, 2018
 - 7 Alexion, Proposed prescribing information for Ultomiris (ravulizumab), October 2, 2018
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6 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MEI-YEAN T CHEN
10/04/2018

CYNTHIA L LACIVITA
10/04/2018