ULTOMIRIS®
(ravulizumab-cwvz)
injection for intravenous use
300 mg/3 mL vial

Sample Appeal Letter for ULTOMIRIS

for Paroxysmal Nocturnal Hemoglobinuria (PNH)

INDICATION

ULTOMIRIS is indicated for the treatment of adult and pediatric patients one month of age and older with paroxysmal nocturnal hemoglobinuria (PNH).

IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

ULTOMIRIS, a complement inhibitor, increases the risk of serious infections caused by *Neisseria meningitidis* [*see Warnings and Precautions (5.1)*]. Life-threatening and fatal meningococcal infections have occurred in patients treated with complement inhibitors. These infections may become rapidly life-threatening or fatal if not recognized and treated early.

- **Complete or update vaccination for meningococcal bacteria (for serogroups A, C, W, Y, and B) at least 2 weeks prior to the first dose of ULTOMIRIS, unless the risks of delaying ULTOMIRIS therapy outweigh the risk of developing a serious infection. Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against meningococcal bacteria in patients receiving a complement inhibitor. See *Warnings and Precautions (5.1)* for additional guidance on the management of the risk of serious infections caused by meningococcal bacteria.**
- **Patients receiving ULTOMIRIS are at increased risk for invasive disease caused by *Neisseria meningitidis*, even if they develop antibodies following vaccination. Monitor patients for early signs and symptoms of serious meningococcal infections and evaluate immediately if infection is suspected.**

Because of the risk of serious meningococcal infections, ULTOMIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called ULTOMIRIS and SOLIRIS REMS [*see Warnings and Precautions (5.2)*].

Please see Important Safety Information on pages 1 and 17-18 and accompanying full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections.

Introduction

When a payer (health plan or pharmacy benefit manager [PBM]) denies a prior authorization (PA), precertification, or reauthorization request for ULTOMIRIS prescribed for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), your patient has the right to appeal the decision. If your patient wishes to appeal, you and your staff may assist by submitting an appeal letter and supporting documentation.

As part of the appeals process, payers may request additional documentation from you to support coverage of ULTOMIRIS when approval for its use has been denied. Your letter should explain why ULTOMIRIS is medically necessary for the specific patient and may include supporting documentation. The letter may be submitted in response to the denial letter or to a payer's request for additional documentation. The letter should include patient-specific information, address the reason for denial, be presented on the prescriber's letterhead, and be signed by the prescriber. The provided sample appeal letter gives you a framework for composing an appeal.

This sample appeal letter is provided for informational purposes only and is not legal advice or official guidance from payers. It is not intended to increase or maximize reimbursement by any payer. Alexion does not warrant, promise, guarantee, or make any statement that the use of this information will result in coverage or payment for ULTOMIRIS or that any payment received will cover providers' costs.

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General Tips for Completing an Appeal Letter

Understand the appeals process for the specific payer. It's important to follow the payer's guidelines when submitting an appeal. Payers may have their own appeal request forms, which are usually available on their website. If a form is required, include it with your own letter. Be sure to contact the payer with any questions and to obtain written instructions for their appeals process.

When submitting an appeal, timing is critical. Refer to the denial letter to find the timelines for submitting the appeal and any payer-specific guidelines.

In cases of medical urgency, your patient may request an expedited review and can expect to receive a decision within 72 hours. For more information, please visit HealthCare.gov.

Understand the reason for denial. It's important to read the denial letter carefully to understand the reason(s) provided. You may also call the payer to discuss a denial with them; this may help inform you about ways to resolve it in a timely manner.

- **If the denial is due to inaccurate or incomplete information,** carefully review the PA or reauthorization request that you submitted to identify information that is incorrect or was omitted. Resubmit the PA or reauthorization request when all the required information is accurate and complete.
- **If there is a medical reason for the denial,** ensure that your appeal letter includes specific and relevant medical information to support ULTOMIRIS use according to the payer's criteria. Your letter should clearly explain why you believe ULTOMIRIS is the most appropriate option for this patient.

Provide all supporting documentation at the same time and in the requested order, as shown in the individual payer's appeal instructions. This might include:

- The payer's appeal form (if required)
- Your appeal letter
- A copy of the payer's denial letter
- Supporting documentation, such as clinical notes, lab results, etc

For more information on the overall appeals process, please refer to the **Alexion ULTOMIRIS Access and Reimbursement Guide**

Our dedicated Field Reimbursement Managers (FRMs) can work with you

In the event of a PA denial, FRMs can provide you or your office staff with educational support and guidance. FRMs can help with:

- Payer options for PA resubmission, including details about the resubmission process, peer-to-peer review, appeals process, and associated timelines
- Review of the redacted denial letter or Explanation of Benefits (EOB) letter to provide specific guidance on next steps and best practices

[John Doe, MD]
[Address]
[City, State ZIP Code]
[(888) 555-5555]

SAMPLE ONLY
Please copy onto your letterhead.

[Date]
[Contact Name], [Title]
[Name of Health Insurance Plan or PBM]
[Address]
[City, State ZIP Code]

Re: [First/Second]-Level Appeal for Coverage Denial of ULTOMIRIS® (ravulizumab-cwvz)
[Request for Expedited Review Due to Medical Urgency]

Denial Letter Date: [MM/DD/YYYY]
Denial Reference #: [Denial Reference #]

Patient: [Name]
Date of Birth: [MM/DD/YYYY]
Member ID Number: [Insurance ID Number] Group Number: [Insurance Group Number]
Rx Bin: [Rx Bin Number] Rx PCN: [Rx PCN Number] Rx Group: [Rx Group Number]

Dear [Contact Name],

I am writing to appeal the coverage denial for [Name of patient]'s treatment with ULTOMIRIS® (ravulizumab-cwvz) for paroxysmal nocturnal hemoglobinuria (PNH). In the letter referenced above, you stated that the reason for denial was [insert reason for denial: eg, a requirement of a history of trial/failure of, contraindication, or intolerance to pegcetacoplan, iptacopan, crovalimab, eculizumab-aagh, or eculizumab-aeeb therapy, lack of transfusion history, low thromboembolic risk]. This letter provides information about my patient's medical history and my treatment rationale.

1 REASON(S) FOR DENIAL AND TREATMENT RATIONALE

In the appeal letter, you will need to address every denial reason(s) stated in the denial letter from the insurance plan. Provide a clear rationale and explain why you disagree with the denial reason. Refer to "Treatment Rationale to Support Appeal" on pages 6-14.

If applicable, describe your patient's treatment goals and your rationale why a step therapy through pegcetacoplan, iptacopan, crovalimab, eculizumab-aagh, or eculizumab-aeeb is not optimal for meeting these goals. Clearly explain why you have concerns regarding the requirement that your patient must have a history of trial/ failure of, contraindication, or intolerance to pegcetacoplan, iptacopan, crovalimab, eculizumab-aagh, or eculizumab-aeeb. Refer to "Treatment Rationale to Support Appeal" on pages 7-12.

In my medical opinion, ULTOMIRIS remains the most appropriate treatment for [Name of patient]. The stated reason(s) for denial was [insert each denial reason and address each reason point by point, referring to "Treatment Rationale to Support Appeal," "Rationale for Reauthorization for Patients Currently Receiving ULTOMIRIS," and "Attachments and Supporting Documentation" on pages 6-16; provide any laboratory results if applicable].

[John Doe, MD]
[Address]
[City, State ZIP Code]
[(888) 555-5555]

SAMPLE ONLY
Please copy onto your letterhead.

2 **SUMMARY AND OPTIONAL MEDICAL HISTORY**

After addressing each stated reason for denial, you may wish to summarize your appeal and restate your patient's relevant medical history and laboratory results.

As stated in my initial authorization request, [Name of patient] is currently [treatment-naïve or stable on the current eculizumab or ravulizumab regimen].

Based on my assessment of their current clinical symptoms and labs, they require [insert recommendation for addressing patient's current therapeutic needs (eg, effective long-term control of the PNH drastic manifestations including: acute resolution of hemolytic crisis or thrombotic symptoms, terminal complement inhibition to reduce risks of intravascular hemolysis, maintenance of stable regimen, and reduction in barriers to adherence)] for which ULTOMIRIS treatment is medically necessary.

Note: Payer policies may require physician attestation regarding the discussion of alternative treatment options and shared decision-making of a PNH treatment plan with patients previously or currently treated with ULTOMIRIS. To fulfill these requirements for continued use of ULTOMIRIS, the following text must be included in the appeal.

I have counseled the patient on alternative chronic treatment options with PNH. My patient has shared in the decision-making process regarding their PNH therapy plan. Collectively, we have determined that ULTOMIRIS is the most clinically appropriate treatment choice for managing their PNH at this time.

For the above reasons, I request that you reverse the coverage determination.

3 For your additional information, I am enclosing [list enclosures, such as a copy of the denial letter, supporting clinical documentation, etc]. If you have any further questions, please feel free to call me at [physician's telephone number] to discuss.

Thank you in advance for your immediate attention to this request.

[Physician's Name], MD
[Physician's Identification Number]
[Physician's Practice Name]
[Physician's Phone Number]
[Physician's Fax Number]
[Physician's Email]

Enclosures
At the bottom of your letter, list the items you have enclosed. Be sure to include every article that you referenced or any new documentation.

1 Treatment Rationale to Support Appeal

In your appeal letter, you may choose to include some of the reasons below for justification. Be sure to attach the supporting references and any additional documentation in your reply.

- **Denial due to indication:** ULTOMIRIS® (ravulizumab-cwvz) is indicated for the treatment of adult and pediatric patients one month of age and older with paroxysmal nocturnal hemoglobinuria (PNH).[1]
- **Denial due to meningococcal vaccinations:** Provide documentation of initial series and/or most recent booster(s) for MenACWY, MenABCWY, and MenB vaccinations. If vaccinations are pending approval of therapy, please include a scheduled date for patient to receive the vaccinations.
- **Denial due to transfusion history:**
  - o If patient has had transfusions:
    - Provide documentation of history of red blood cell/white blood cell transfusions [number of infusions, dates, as well as the units transfused].
  - o If patient has not had a history of transfusions, please use the following statement to support your appeal:
    - [Patient name] does not have a history of transfusions. Based on the inclusion criteria of the two pivotal trials for ULTOMIRIS, Study 301 and Study 302, patients were not required to have a history of transfusions to qualify for treatment with ULTOMIRIS.[2,3] In Study 301 and Study 302, 18% of patients and 87% patients treated with ULTOMIRIS were transfusion naïve, respectively.[4,5]
- **Denial due to patient not meeting thrombotic risk (no clot or clone size is too small, no thrombotic event):**
  - o If patient has had a thrombotic event:
    - Provide documentation of history of thromboembolic events and symptoms of thrombosis [neurologic symptoms, abdominal pain, leg swelling], laboratory or imaging results confirming diagnosis [elevated D-dimer, magnetic resonance imaging (MRI), computer tomography (CT), and/or PNH clone size (indicative of risk for thromboembolic events)].
  - o If patient has not had a thrombotic event, please use the following statement to support your appeal:
    - Even though [patient name] has not had a thrombotic event, [patient name] is at increased risk to potentially experience a thrombotic event due to [elevated LDH (LDH ≥1.5 x ULN) and/or clinical symptoms (abdominal pain, chest pain, and dyspnea), or other indicators of increased risk of thrombotic events]. Thromboembolism is the most common cause of mortality in patients with PNH and accounts for approximately 40% to 67% of PNH-related deaths of which the cause is known.[6] The risk of further thrombotic events increases after the initial incident, with a five to ten times increase in mortality. Furthermore, 25% of thrombotic events are fatal and 20.5% involve more than one site.[7] With the risk of thrombotic events occurring in patients with PNH, in my medical opinion, I believe it would be in the best interest of [patient name] to remain on ULTOMIRIS as incidence of thrombotic events was low in patients taking ULTOMIRIS over the course of 2 years (ie, 0.7%, n=3/434).[8]
- **Denial due to omission of necessary lab results:** Provide any appropriate or confirmatory lab values [evidence of lactate dehydrogenase (LDH) level ≥1.5 times the upper limit of normal, abnormal high sensitivity flow cytometry results, negative direct antiglobulin or Coombs' test, elevated reticulocytes, decreased levels of hemoglobin, or decreased levels of serum haptoglobin].

Click here to see supporting rationale for the required use of ULTOMIRIS

1 Treatment Rationale to Support Appeal (cont'd)

- **Denial due to required step therapy:** Please see respective sections below for supporting statements against the use of step therapy through pegcetacoplan, iptacopan, crovalimab, eculizumab-aagh, or eculizumab-aeeb:

Click here to see denial due to required use of pegcetacoplan | Click here to see denial due to required use of iptacopan | Click here to see denial due to required use of crovalimab | Click here to see denial due to required use of eculizumab-aagh | Click here to see denial due to required use of eculizumab-aeeb

  - **Denial due to required use of pegcetacoplan:** In my medical opinion, pegcetacoplan is not an appropriate step for my patient based on the following relevant clinical criteria [below is a list of potential considerations why pegcetacoplan may not be appropriate for your patient given their case or specific clinical presentation. One or more of these reasons may apply to your patient's individual case].
    - **Patient requires acute treatment for hemolytic crisis or thrombotic symptoms**
      [Name of patient] is currently experiencing [an acute hemolytic crisis or acute thrombotic symptoms] based on [insert laboratory and clinical data supporting diagnosis (eg, predisposing patient factors, platelet counts indicative of severe thrombocytopenia, elevated D-dimer, and/or history of prior deep vein thrombosis)].[9,10] According to the prescribing information, it took 4 to 6 weeks for pegcetacoplan to achieve steady-state serum concentrations following the first dose.[11] In my medical opinion, pegcetacoplan will not mitigate this acute crisis.
    - **Patient is complement inhibitor–naïve and their flow cytometry results show a clone size of 5%-9%**
      [Name of patient] has a diagnosis of PNH confirmed by high-sensitivity flow cytometry with the clone size 5%-9%. In my medical opinion, pegcetacoplan is not an appropriate step for my patient as they would not have been included in the PRINCE study (complement inhibitor–naïve trial).[12]
    - **Patient is under 18 years of age**
      [Name of patient] is [age] years old. Pegcetacoplan is not indicated for pediatric patients under age 18.[11]
    - **Health risk in performing or adhering to self-injection due to physical and/or cognitive impairment**
      In my opinion [Name of patient] is unlikely to be able to perform the steps necessary to regularly self-administer pegcetacoplan given [insert complicating factors that may contribute to nonadherence to pegcetacoplan (physical and mental impairments, reduced functional capacity, lack of psychosocial or caregiver support, patient lifestyle)]. Pegcetacoplan administration requires patients to self-administer twice weekly subcutaneous infusions via an infusion pump.[11] In my medical opinion, given this route of administration I do not believe that [Name of patient] can successfully adhere to this treatment regimen.

1 Treatment Rationale to Support Appeal (cont'd)

PEGASUS Study Design – Select Patient Inclusion Criteria

In my medical opinion, pegcetacoplan is not an appropriate step for my patient as they would not have been included in the PEGASUS phase 3 clinical trial based on the following select relevant study inclusion criteria. [List specific reason(s) based on provided select 'PEGASUS Study – Select Patient Inclusion Criteria' below][13,14]

- Patients with hemoglobin level <10.5 g/dL despite treatment with stable doses of eculizumab for ≥3 months prior to screening[13,14]
- Patients were required to have reticulocytes >1.0 × the upper limit of normal (ULN), platelets >50 × 10^9/L, and neutrophils >0.5 × 10^9/L[13,14]
- Participants were also required to have <35.0 kg/m^2 in body mass index[13,14]

PRINCE Study Design – Select Patient Inclusion Criteria

In my medical opinion, pegcetacoplan is not an appropriate step for my patient as they would not have been included in the PRINCE phase 3 clinical trial based on the following select relevant study inclusion criteria. [List specific reason(s) based on provided select 'PRINCE Study – Select Patient Inclusion Criteria' below][12]

- Hemoglobin level below the lower limit of normal (LLN) (male: <13.6 g/dL and female: <12.0 g/dL)[12]
- Ferritin levels ≥LLN (≥13 ng/mL) or total iron binding capacity ≤ULN (≤155 µg/dL)[12]
- A body mass index ≤35 kg/m^2, platelets >50,000/mm^3, and >500/mm^3 in absolute neutrophil count[12]
- PNH diagnosis confirmed by high-sensitivity flow cytometry (granulocyte or monocyte clone >10%)[12]

1 Treatment Rationale to Support Appeal (cont'd)

- **Denial due to required use of iptacopan:** In my medical opinion, iptacopan is not an appropriate step for my patient based on the following relevant clinical criteria [below is a list of potential considerations why iptacopan may not be appropriate for your patient given their case or specific clinical presentation. One or more of these reasons may apply to your patient's individual case].
  - **Patient is under 18 years of age**
    [Name of patient] is [age] years old. Iptacopan is not indicated for pediatric patients under age 18.[15]
  - **Patient has a lipid disorder and/or a history of a lipid disorder**
    Iptacopan increases total cholesterol, low-density lipoprotein (LDL)-cholesterol, and serum triglycerides, and some patients required cholesterol-lowering medications throughout the iptacopan clinical trials. Further, in the APPLY-PNH clinical trial for iptacopan, 6% (4/62) of the patients in the iptacopan group vs 0% in the anti-C5 inhibitor group had a lipid disorder (ie, dyslipidemia, blood cholesterol increased, low-density lipoprotein increased, hypercholesterolemia, blood triglycerides increased, hyperlipidemia). In the APPOINT-PNH trial, 8% (3/40) of the patients in the iptacopan group had a lipid disorder.[15]

    In my medical opinion, iptacopan is not an appropriate step for my patient as they [have a lipid disorder/have a past medical history of a lipid disorder] and will require more close monitoring of lipid parameters periodically and may require interventions to treat their lipid disorder during treatment.[15]

    My patient has elevated serum transaminases. Increases in serum transaminases have been reported with patients on lipid-lowering statin medications. In my medical opinion, iptacopan would not be an appropriate step therapy for my patient because treatment with iptacopan may require my patient to start treatment with a lipid-lowering medication and may further increase my patient's serum transaminase levels.[15-17]
  - **Patient has thrombocytopenia and/or a history of thrombocytopenia**
    In the APPLY-PNH clinical trial for iptacopan, 6% (4/62) of the patients in the iptacopan group vs 0% in the anti-C5 (SOLIRIS and ULTOMIRIS) group had thrombocytopenia.[15] In my medical opinion, iptacopan is not an appropriate step for [Name of patient] as they currently have laboratory evidence of thrombocytopenia with a platelet count of [insert platelet count] [and/or a past medical history of thrombocytopenia].
  - **Patient is taking a CYP2C8 inducer and/or a CYP2C8 inhibitor**
    CYP2C8 inducers (eg, rifampin) may decrease iptacopan exposure, which may result in loss of or reduced efficacy of iptacopan.[15] In my medical opinion, iptacopan is not an appropriate step for [Name of patient] as they are currently on a CYP2C8 inducer, [Name of CYP2C8 inducer], and will require additional monitoring for loss of efficacy of iptacopan.[15] Further, if the loss of efficacy of iptacopan becomes evident, the patient may have to go through the potential dose adjustments and/or discontinuation of [Name of CYP2C8 inducer] that they are currently stable on.[15]

    Strong CYP2C8 inhibitors (eg, gemfibrozil) may increase iptacopan exposure, which may result in an increased risk for adverse reactions with iptacopan.[15] Therefore, coadministration of iptacopan with CYP2C8 inhibitors is not recommended.[15] In my medical opinion, iptacopan is not an appropriate step for [Name of patient] as they are currently on a strong CYP2C8 inhibitor, [Name of strong CYP2C8 inhibitor], putting them at risk for increased adverse reactions of iptacopan such as hyperlipidemia.[15]
  - **Iptacopan lacks real-world evidence**
    As iptacopan was recently approved in 2023, iptacopan lacks real-world evidence.[18] [Name of patient] and I prefer to use a therapy, such as ULTOMIRIS, that has real-world evidence, 6 years of approved use, and shows substantial and demonstrated established safety and efficacy to patients.[1]

1 Treatment Rationale to Support Appeal (cont'd)

- **Health risk in performing or adhering to self-administration of a twice-daily oral dosing regimen due to history of medication nonadherence**

  In my medical opinion [Name of patient] is unlikely to be able to perform the steps necessary to adhere to iptacopan oral intake given [insert complicating factors that may contribute to nonadherence to iptacopan (history of nonadherence to oral medications, physical and mental impairments, reduced functional capacity, lack of psychosocial or caregiver support, patient lifestyle)]. Iptacopan administration requires patients to self-administer twice-daily oral medications.[15] Given this route of administration, I do not believe that [Name of patient] can successfully adhere to this treatment regimen. Iptacopan has a short half-life (~25 hours) and may not be a good choice for patients who have a history of medication nonadherence. Missed doses, especially in the setting of complement-amplifying conditions such as infections or excessive consumption of alcohol, could lead to hemolysis and risk for thrombosis.[15,19]

- **Patient's flow cytometry results show a clone size of 5%-9%**
  [Name of patient] has a diagnosis of PNH confirmed by high-sensitivity flow cytometry with the clone size 5%-9%. In my medical opinion, iptacopan is not an appropriate step for my patient as they would not have been included in the APPLY-PNH or APPOINT-PNH study.[20,21]

- **Patient has laboratory evidence of bone marrow failure**
  [Name of patient] has laboratory evidence of bone marrow failure (reticulocytes <100x10E9/L; platelets <30x10E9/L; neutrophils <500x10E6/L). In my medical opinion, iptacopan is not an appropriate step for my patient as they would not have been included in the APPLY-PNH or APPOINT-PNH studies.[20,21]

APPLY-PNH Study Design – Select Patient Inclusion Criteria

In my medical opinion, iptacopan is not an appropriate step for my patient as they would not have been included in the APPLY-PNH phase 3 clinical trial based on the following select relevant study inclusion criteria. [List specific reason(s) based on provided select 'APPLY-PNH Study – Select Patient Inclusion Criteria' below][20]

- Mean hemoglobin level <10 g/dL[20]
- Diagnosis of PNH confirmed by high-sensitivity flow cytometry with the clone size ≥10%[20]

APPOINT-PNH Study Design – Select Patient Inclusion Criteria

In my medical opinion, iptacopan is not an appropriate step for my patient as they would not have been included in the APPOINT-PNH phase 3 clinical trial based on the following select relevant study inclusion criteria. [List specific reason(s) based on provided select 'APPOINT-PNH Study – Select Patient Inclusion Criteria' below][21]

- Mean hemoglobin level <10 g/dL[21]
- Diagnosis of PNH confirmed by high-sensitivity flow cytometry with the clone size ≥10%[21]

1 Treatment Rationale to Support Appeal (cont'd)

- **Denial due to required use of crovalimab:** In my medical opinion, crovalimab is not an appropriate step for my patients based on the following relevant clinical criteria [below is a list of potential considerations why crovalimab may not be appropriate for your patient given their case or specific clinical presentation. One or more of these reasons may apply to your patient's individual case].
  - **Patient is under 13 years of age**

    [Name of patient] is [age] years old. Crovalimab is not indicated for pediatric patients under age 13.[22]
  - **Nonadherence due to a history of aversion to needle injections**

    In my medical opinion, [Name of patient] is unlikely to be able to adhere to the multiple injections required of crovalimab's maintenance dose given [insert complicating factors that may contribute to nonadherence to crovalimab (history of aversion to needle injections, experience with severe injection-related reactions, patient lifestyle, physical and mental impairments)]. Crovalimab requires an initial intravenous loading dose and then a minimum of 2 subcutaneous injections, thereafter, for maintenance dosing.[22] Given this route of administration, I do not believe [Name of patient] can successfully adhere to this treatment regimen. Not completing all doses may result in different efficacy results as seen in the COMMODORE 2 clinical trial as patients were given 2 to 3 subcutaneous injections every 4 weeks, depending on their weight, for maintenance dosing.[22]
  - **Risk of Type III hypersensitivity reactions due to the formation of drug-target-drug complexes (DTDC) when switching between C5 therapies**

    [Name of patient] is currently being treated for PNH with ULTOMIRIS. When switching between C5 therapies that bind to different C5 epitopes, such as in the case of crovalimab and ULTOMIRIS, DTDCs could form.[23] In clinical trials, Type III hypersensitivity reactions were reported in 39 patients (19%, n=201) who switched from eculizumab or ravulizumab to crovalimab. Type III hypersensitivity reactions included arthralgia, rash, pyrexia, myalgia, headache, fatigue, petechiae, and abdominal pain.[22] Among patients who experienced Type III hypersensitivity reactions, 8 patients (21%, n=39) had events that were severe enough to result in hospitalization.[22] Since [Name of patient] is currently clinically stable on ULTOMIRIS as shown with [increased or stabilization of hemoglobin levels, reduction in transfusions, improvement in hemolysis, decrease in LDH],[4,5] [Name of patient] and I have a strong preference to continue using ULTOMIRIS in treating [Name of patient]'s PNH and to avoid the possibility of introducing Type III hypersensitivity reactions.
  - **Patient's flow cytometry results show a clone size of 5% to 9%**

    [Name of patient] has a diagnosis of PNH confirmed by high-sensitivity flow cytometry with the clone size of 5% to 9%. In my medical opinion, crovalimab is not an appropriate step for my patient as they would not have been included in both COMMODORE 1 and COMMODORE 2 studies.[24,25]
  - **Crovalimab lacks real-world evidence**

    As crovalimab was recently approved in 2024, crovalimab lacks real-world evidence.[26] [Name of patient] and I prefer to use a therapy, such as ULTOMIRIS, with real-world evidence, 6 years of approved use, and demonstrated and established safety and efficacy to patients.[1,8]

COMMODORE 1 Study Design—Select Patient Inclusion Criteria

In my medical opinion, crovalimab is not an appropriate step for my patient as they would not have been included in the COMMODORE 1 phase 3 clinical trial based on the following select relevant study inclusion criteria. [List specific reason(s) based on provided select 'COMMODORE 1 Study—Select Patient Inclusion Criteria' below]

- Diagnosis of PNH confirmed by high-sensitivity flow cytometry with a clone size of ≥10%[24]

COMMODORE 2 Study Design—Select Patient Inclusion Criteria

In my medical opinion, crovalimab is not an appropriate step for my patient as they would not have been included in the COMMODORE 2 phase 3 clinical trial based on the following select relevant study inclusion criteria. [List specific reason(s) based on provided select 'COMMODORE 2 Study—Select Patient Inclusion Criteria' below]

- Diagnosis of PNH confirmed by high-sensitivity flow cytometry with a clone size of ≥10%[25]

1 Treatment Rationale to Support Appeal (cont'd)

- **Denial due to required use of biosimilar [eculizumab-aagh or eculizumab-aeeb]:** In my medical opinion, [eculizumab-aagh or eculizumab-aeeb] is not an appropriate step for my patient based on the following relevant clinical criteria [below is a list of potential considerations why eculizumab-aagh or eculizumab-aeeb may not be appropriate for your patient given their case or specific clinical presentation. One or more of these reasons may apply to your patient's individual case].
  - **Non-medical switching**

    [Name of patient] is currently being treated for PNH with ULTOMIRIS. While non-medical switching is a practice becoming more common as biosimilars enter the market, study results regarding similarities in efficacy and safety from different originator-biosimilar combinations cannot be generalized.[27] Based on my medical experience, a non-medical switch could result in potential interrupted therapy due to treatment logistics, increased side effects, and medication abandonment by the patient. Since [Name of patient] is currently clinically stable on ULTOMIRIS as shown with [increased or stabilization of hemoglobin levels, reduction in transfusions, improvement in hemolysis, decrease in LDH],[4,5] the patient and I have a strong preference to continue using ULTOMIRIS in treating [his/her/their] PNH.
  - **Patient is allergic, intolerant, or has a medical condition that is not compatible with excipients present in [eculizumab-aagh or eculizumab-aeeb]**

    The patient is unable to take [eculizumab-aagh or eculizumab-aeeb] due to a[n] [allergic reaction, intolerance, or incompatible medical condition (eg, diabetes)] to [trehalose in eculizumab-aagh[28]; sorbitol, edetate disodium (EDTA), and/or sodium hydroxide in eculizumab-aeeb[29]]. Due to this [allergic reaction, intolerance, or incompatible medical condition (eg, diabetes)], it would be in the patient's best interest to continue using ULTOMIRIS as [he is/she is/they are] are currently stable as shown with [increased or stabilization of hemoglobin levels, reduction in transfusions, improvement in hemolysis, decrease in LDH].[4,5]
  - **Patient is not amendable to biweekly dosing regimen for [eculizumab-aagh or eculizumab-aeeb]**

    [Name of patient] is unable to comply with the maintenance treatment dosing interval of every 2 weeks for [eculizumab-aagh[28] or eculizumab-aeeb[29]] because of [fill in reason for patient being unable to reach office for infusion (eg, lack of transportation, job scheduling, other personal obligations)]. Currently, [Name of patient] can maintain the dosing interval schedule of every [4 weeks (ie, for patient weighing 5 kg to <20 kg) or 8 weeks (ie, for patients weighing 20 kg to >100 kg)] for ULTOMIRIS.[1]
  - **[eculizumab-aagh or eculizumab-aeeb] lacks real-world evidence**

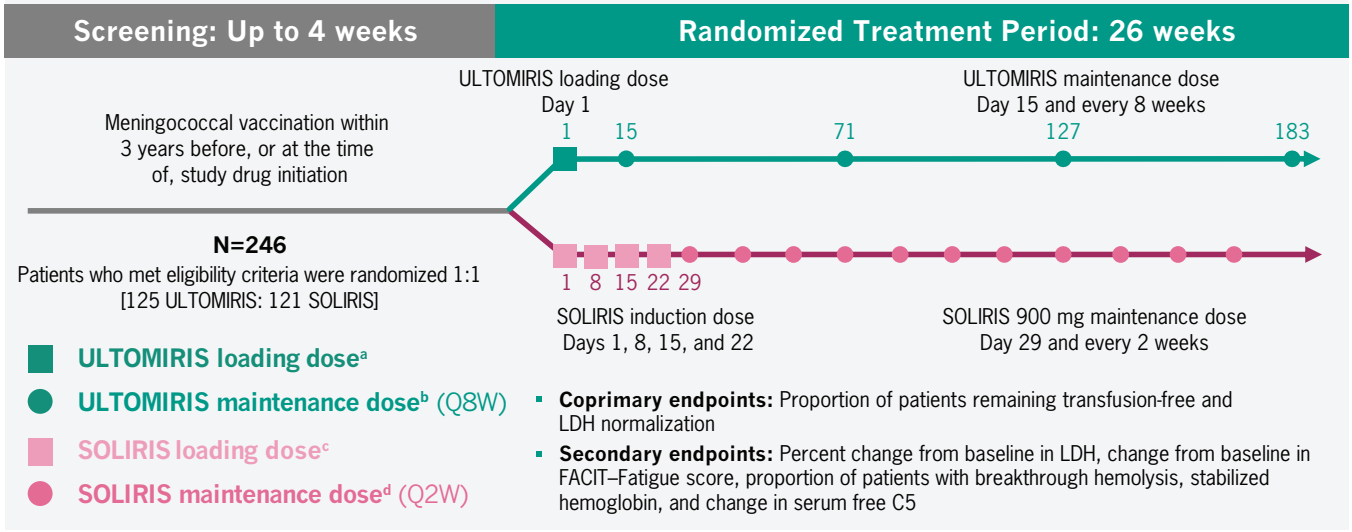
    As [eculizumab-aagh[30] or eculizumab-aeeb[31]] was recently approved in 2024, [eculizumab-aagh or eculizumab-aeeb] lacks real-world evidence. [Name of patient] and I prefer to use a therapy, such as ULTOMIRIS, with real-world evidence, 6 years of approved use, and demonstrated and established safety and efficacy to patients.[1,8]

1 Treatment Rationale to Support Appeal (cont'd)

Rationale for required use of ULTOMIRIS® (ravulizumab-cwvz)

Study 301: Phase 3, open-label, randomized, non-inferiority, active-controlled trial evaluating the efficacy and safety of ULTOMIRIS in 246 complement inhibitor–naïve adult patients with PNH who received ULTOMIRIS (N=125) or SOLIRIS® (eculizumab) (N=121).[4]

THE FOLLOWING EFFICACY AND SAFETY DATA ARE BASED ON THE TRIAL DESIGN BELOW.



Key: FACIT, Functional Assessment of Chronic Illness Therapy; **LDH,** lactate dehydrogenase; **Q2W,** every 2 weeks; **Q8W,** every 8 weeks.
[a]ULTOMIRIS loading dose = 2400 mg for patients weighing ≥40 kg to <60 kg, 2700 mg for patients weighing ≥60 kg to <100 kg, 3000 mg for patients weighing ≥100 kg. [b]ULTOMIRIS maintenance dose = 3000 mg for patients weighing ≥40 kg to <60 kg, 3300 mg for patients weighing ≥60 kg to <100 kg, 3600 mg for patients weighing ≥100 kg. [c]SOLIRIS induction dose = 600 mg (Study 301 only). [d]SOLIRIS maintenance dose = 900 mg.

- ULTOMIRIS is a complement inhibitor that is Food and Drug Administration (FDA) approved for treatment of PNH in adult and pediatric patients 1 month of age and older[1]
- ULTOMIRIS achieved complete terminal complement inhibition (defined as serum-free C5 <0.5 µg/mL) by the end of the first infusion, which was sustained throughout the treatment period in all patients[4]
- Proportions of patients with breakthrough hemolysis were 4.0% in the ULTOMIRIS group vs 10.7% in the SOLIRIS group (difference, −6.7% [95% confidence interval (CI): −14.21, 0.18]; P_{inf} <.0001)[4]
  - Breakthrough hemolysis (BTH) rates remained low (<7%) at 2 years of ULTOMIRIS treatment[8]
- 73.6% of patients receiving ULTOMIRIS and 66.1% receiving SOLIRIS avoided transfusion, with a between-group difference of 6.8% (95% CI: −4.66, 18.14; P_{inf} <.0001). The lower bound of the 95% CI was greater than the protocol-specified non-inferiority margin of −20%[4]
  - A majority of the patients (~73%) achieved transfusion avoidance at 2 years of treatment with ULTOMIRIS[8]
- The adjusted prevalence of LDH normalization was 53.6% for the ULTOMIRIS group and 49.4% for the SOLIRIS group; the adjusted odds ratio (OR) for comparison of ULTOMIRIS vs SOLIRIS was 1.19 (95% CI: 0.80, 1.77; P_{inf} <.0001). The lower bound of the 95% CI was greater than the protocol-specified non-inferiority margin of 0.39[4]
  - A majority of the patients (>90%) achieved and maintained LDH ≤1.5 upper limit of normal (ULN) through 2 years of treatment with ULTOMIRIS[8]
- ULTOMIRIS has an established safety profile[1]
- ULTOMIRIS is a terminal complement inhibitor that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the terminal complement complex [C5b-9]) and preventing the generation of the terminal complement complex C5b-9. ULTOMIRIS inhibits terminal complement–mediated intravascular hemolysis in patients with PNH[1]

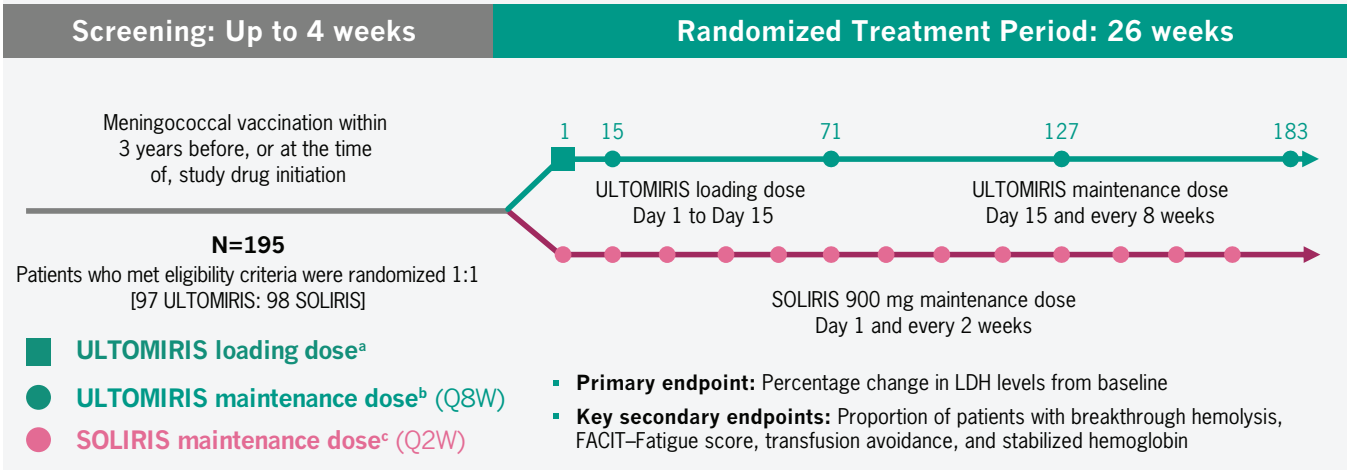
Please see Important Safety Information on pages 1 and 17-18 and accompanying full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections.

ULTOMIRIS® (ravulizumab-cwvz) injection for intravenous use 300 mg/3 mL vial

1 Treatment Rationale to Support Appeal (cont'd)

Study 302: Phase 3, open-label, randomized, non-inferiority, active-controlled trial evaluating the efficacy and safety of ULTOMIRIS® (ravulizumab-cwvz) in 195 adult patients with PNH who were stable on SOLIRIS® (eculizumab) and received ULTOMIRIS (N=97) or SOLIRIS (N=98).[5]

THE FOLLOWING EFFICACY AND SAFETY DATA ARE BASED ON THE TRIAL DESIGN BELOW.



Key: FACIT, Functional Assessment of Chronic Illness Therapy; **LDH,** lactate dehydrogenase; **Q2W,** every 2 weeks; **Q8W,** every 8 weeks. [a]ULTOMIRIS loading dose = 2400 mg for patients weighing ≥40 kg to <60 kg, 2700 mg for patients weighing ≥60 kg to <100 kg, 3000 mg for patients weighing ≥100 kg. [b]ULTOMIRIS maintenance dose = 3000 mg for patients weighing ≥40 kg to <60 kg, 3300 mg for patients weighing ≥60 kg to <100 kg, 3600 mg for patients weighing ≥100 kg. [c]SOLIRIS maintenance dose = 900 mg.

- ULTOMIRIS is a complement inhibitor that is FDA approved for treatment of PNH in adult and pediatric patients 1 month of age and older[1]
- Mean serum-free C5 concentrations were suppressed to <0.5 µg/mL by the end of the first infusion and at all subsequent visits for all patients receiving ULTOMIRIS[5]
- No patients in the ULTOMIRIS group experienced breakthrough hemolysis compared with 5 (5.1%) patients in the SOLIRIS group (difference, 5.1% [95% CI: -8.89%, 18.99%; P_{inf} <.0004])[5]
  - BTH rates remained low (<7%) at 2 years of ULTOMIRIS treatment[8]
- 87.6% of patients in the ULTOMIRIS group remained transfusion-free by the end of the randomization period compared with 82.7% of patients in the SOLIRIS group, with a between-group difference of 5.5% (95% CI: −4.27%, 15.68%; P_{inf} <.0001)[5]
  - A majority of the patients (~85%) achieved transfusion avoidance at 2 years of ULTOMIRIS treatment[8]
- The least-squares estimate of the mean in percentage change in LDH from baseline showed a decrease of 0.82% (3.033%) for the ULTOMIRIS group and an increase of 8.39% (3.041%) for the SOLIRIS group, with a treatment difference of 9.21% (95% CI: −0.42%, 18.84%). The lower bound of the 95% CI for the difference was −0.42%, which exceeded the protocol-specified non-inferiority margin of −15%, indicating that ULTOMIRIS is non-inferior to SOLIRIS with a P_{inf} <.0006[5]
  - ≥95% of patients achieved LDH ≤1.5 × ULN at 26 weeks and maintained this through 2 years of treatment with ULTOMIRIS[8]
- ULTOMIRIS has an established safety profile[1]
- ULTOMIRIS is a terminal complement inhibitor that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the terminal complement complex [C5b-9]) and preventing the generation of the terminal complement complex C5b-9. ULTOMIRIS inhibits terminal complement–mediated intravascular hemolysis in patients with PNH[1]

Rationale for Reauthorization for Patients Currently Receiving ULTOMIRIS® (ravulizumab-cwvz)

Health plans often require a prior authorization (PA) for patients receiving specialty medications and orphan drugs treating rare diseases. In many cases, after a patient has received a PA, the patient will need a reauthorization (sometimes known as a renewal authorization) after a specified time period. Obtaining a reauthorization for your patient is often required to confirm that the drug continues to be medically necessary and that the patient has responded to therapy.

- **Denial due to new documentation not previously required:**
  The reauthorization requirements for [Name of patient] have changed since they were initially authorized for treatment with ULTOMIRIS. [List of additional documentation that is now required] is now required to obtain reapproval for ULTOMIRIS. I am requesting a medical exception to continue [Name of patient]'s current treatment based on the original authorization criteria because they have had a demonstrated clinical improvement as evidenced by [insert demonstrated clinical response rationale and/or documentation].

- **Denial due to specific reauthorization clinical improvement criteria:**
  In my medical opinion, [Name of patient] is currently responding positively to treatment with ULTOMIRIS as evidenced by [list specific measures such as: improvement in hemolysis, decrease in lactate dehydrogenase (LDH), reduced need for red blood cell (RBC) transfusions, increased or stabilization of hemoglobin levels, fewer thrombotic events].[4,5] Although [Name of patient] may partially meet [list specific denial reason/specified lab result or clinical measure] reauthorization criteria, I believe ULTOMIRIS is still the optimal therapy for reaching this patient's treatment goals of [controlling intravascular hemolysis (IVH), preventing thrombosis, reducing breakthrough hemolysis, decreasing end organ damage].[6,32-40]

- **Denial due to change in policy required step edit:**
  [Name of patient] was diagnosed with PNH on [date] and has received ULTOMIRIS treatment since [date of first infusion]. [Name of patient] received authorization for ULTOMIRIS based on initial prior authorization criteria. [He is/She is/They are] currently responding positively to treatment with ULTOMIRIS as demonstrated by [increased or stabilization of hemoglobin levels, reduction in transfusions, improvement in hemolysis, decrease in LDH].[4,5] [He is/She is/They are] currently stable on this treatment regimen, and it would be clinically inappropriate to require them to stop treatment with ULTOMIRIS or switch to another therapy given the risk of [hemolysis, thrombosis, hematologic instability, decline in renal function, pulmonary hypertension, and/or end organ damage].[6,32-40]

2 Optional Medical History

You may find it helpful to include a brief impactful medical history in your patient's appeal letter with only the most clinically significant facts repeated, such as:

- Lab results confirming diagnosis of PNH
  - Clinical, imaging, and antibody findings including high-sensitivity flow cytometry confirming PNH with a granulocyte or monocyte clone size ≥5%
  - LDH level ≥1.5 times the upper limit of normal
- Clinical rationale for initiating ULTOMIRIS in this patient
  - History of transfusions
  - Evidence of acute hemolytic crisis or thrombotic symptoms (ie, platelet counts indicative of severe thrombocytopenia, elevated D-dimer, and/or history of prior deep vein thrombosis)
  - Impact of PNH on patient's level of physical function
  - Health risk in performing self-injection due to physical and/or cognitive impairment (ie, physical and mental impairments, reduced functional capacity, and lack of psychosocial or caregiver support)

3 Attachments and Supporting Documentation

In the appeal, you only need to include the original appeal letter and new supporting documentation. If you referred to any specific articles or obtained any photographs or attestations, be sure to attach them to the appeal.

Additional resources that may be used in submitting your letter of appeal may include the ULTOMIRIS Prescribing Information, original denial letter, ULTOMIRIS Letter of Medical Necessity, ULTOMIRIS Access and Reimbursement Guide.

For additional access resources, please visit:

Explore Alexion Access Navigator

ALEXION ACCESS NAVIGATOR

Alexion Access Navigator is a dedicated resource website for US Healthcare Professionals and their offices that contains downloadable access and reimbursement materials for ULTOMIRIS® (ravulizumab-cwvz).

Online: https://alexionaccessnavigator.com

References: 1. ULTOMIRIS. Prescribing Information. Alexion Pharmaceuticals, Inc. **2.** Lee JW, Sicre de Fontbrune F, Wong Lee Lee L, et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. *Blood.* 2019;133(6):530-539. **3.** Kulasekararaj AG, Hill A, Rottinghaus ST, et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. *Blood.* 2019;133(6):540-549. **4.** Lee JW, Sicre de Fontbrune F, Wong Lee Lee L, et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. *Blood.* 2019;133(6):530-539. **5.** Kulasekararaj AG, Hill A, Rottinghaus ST, et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitorexperienced adult patients with PNH: the 302 study. *Blood.* 2019;133(6):540-549. **6.** Hill A, Kelly RJ, Hillmen P. Thrombosis in paroxysmal nocturnal hemoglobinuria. *Blood.* 2013;121(25):4985-4996. **7.** Malato A, Saccullo G, Coco LL, et al. Thrombotic complications in paroxysmal nocturnal haemoglobinuria: a literature review. *Blood Transfus.* 2012;10(4):428-435. **8.** Kulasekararaj AG, Griffin M, Langemeijer S, et al. Long-term safety and efficacy of ravulizumab in patients with paroxysmal nocturnal hemoglobinuria: 2-year results from two pivotal phase 3 studies. *Eur J Haematol.* 2022;109(3):205-214. **9.** Hill A, DeZern AE, Kinoshita T, Brodsky RA. Paroxysmal nocturnal haemoglobinuria. *Nat Rev Dis Primers.* 2017;3:17028. **10.** Brodsky RA. Treatment and prognosis of paroxysmal nocturnal hemoglobinuria. UpToDate. Updated November 6, 2024. Accessed November 15, 2024. https://www.uptodate.com/contents/treatment-and-prognosis-of-paroxysmal-nocturnal-hemoglobinuria **11.** EMPAVELI. Prescribing Information. Apellis Pharmaceuticals, Inc. **12.** Wong RSM, Navarro-Cabrera JR, Comia NS, et al. Pegcetacoplan controls hemolysis in complement inhibitor-naive patients with paroxysmal nocturnal hemoglobinuria. *Blood Adv.* 2023;7(11):2468-2478. **13.** Hillmen P, Szer J, Weitz I, et al. Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med.* 2021;384(11):1028-1037. **14.** Hillmen P, Szer J, Weitz I, et al. Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med.* 2021;384(11):1028-1037. Accessed November 15, 2024. https://www.nejm.org/doi/suppl/10.1056/NEJMoa2029073/suppl_file/nejmoa2029073_appendix.pdf **15.** FABHALTA. Prescribing Information. Novartis AG. **16.** LIPITOR. Prescribing Information. Viatris Inc. **17.** CRESTOR. Prescribing Information. AstraZeneca. **18.** US Food and Drug Administration. Department of Health and Human Services. FABHALTA NDA218276 approval letter. December 5, 2023. Accessed November 15, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/218276Orig1s000ltr.pdf **19.** Devalet B, Mullier F, Chatelain B, Dogne JM, Chatelain C. Pathophysiology, diagnosis, and treatment of paroxysmal nocturnal hemoglobinuria: a review. *Eur J Haematol.* 2015;95(3):190-198. **20.** ClinicalTrials.gov identifier: NCT04558918. Accessed November 15, 2024. https://clinicaltrials.gov/study/NCT04558918 **21.** ClinicalTrials.gov identifier: NCT04820530. Accessed November 15, 2024. https://classic.clinicaltrials.gov/ct2/show/NCT04820530 **22.** PIASKY. Prescribing Information. Genentech, Inc. **23.** Nishimura JI, Soubret A, Arase N, et al. Mitigating drug-target-drug complexes in patients with paroxysmal nocturnal hemoglobinuria who switch C5 inhibitors. *Clin Pharmacol Ther.* 2023;113(4):904-915. **24.** Scheinberg P, Cle DV, Kim JS, et al. Phase 3 randomized COMMODORE 1 trial: crovalimab versus eculizumab in complement inhibitor-experienced patients with paroxysmal nocturnal hemoglobinuria. *Am J Hematol.* 2024;99(9):1757-1767. **25.** Roth A, He G, Tong H, et al. Phase 3 randomized COMMODORE 2 trial: crovalimab versus eculizumab in patients with paroxysmal nocturnal hemoglobinuria naive to complement inhibition. *Am J Hematol.* 2024;99(9):1768-1777. **26.** US Food and Drug Administration. Department of Health and Human Services. PIASKY BLA761388 approval letter. June 20, 2024. Accessed November 15, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2024/761388Orig1s000ltr.pdf **27.** Feagan BG, Marabani M, Wu JJ, Faccin F, Spronk C, Castaneda-Hernandez G. The challenges of switching therapies in an evolving multiple biosimilars landscape: a narrative review of current evidence. *Adv Ther.* 2020;37(11):4491-4518. **28.** EPYSQLI. Prescribing Information. Samsung Bioepis Co., Ltd. **29.** BKEMV. Prescribing Information. Amgen Inc. **30.** US Food and Drug Administration. Department of Health and Human Services. EPYSQLI BLA761340 approval letter. July 19, 2024. Accessed November 15, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2024/761340Orig1s000ltr.pdf **31.** US Food and Drug Administration. Department of Health and Human Services. BKEMV BLA761333 approval letter. May 28, 2024. Accessed November 15, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2024/761333Orig1s000ltr.pdf **32.** De Latour RP, Mary JY, Salanoubat C, et al. Paroxysmal nocturnal hemoglobinuria: natural history of disease subcategories. *Blood.* 2008;112(8):3099-3106. **33.** Loschi M, Porcher R, Barraco F, et al. Impact of eculizumab treatment on paroxysmal nocturnal hemoglobinuria: a treatment versus no-treatment study. *Am J Hematol.* 2016;91(4):366-370. **34.** Hillmen P, Elebute M, Kelly R, et al. Long-term effect of the complement inhibitor eculizumab on kidney function in patients with paroxysmal nocturnal hemoglobinuria. *Am J Hematol.* 2010;85(8):553-559. **35.** Clark DA, Butler SA, Braren V, Hartman RC, Jenkins DE Jr. The kidneys in paroxysmal nocturnal hemoglobinuria. *Blood.* 1981;57(1):83-89. **36.** Weitz I, Meyers G, Lamy T, et al. Cross-sectional validation study of patient-reported outcomes in patients with paroxysmal nocturnal haemoglobinuria. *Intern Med J.* 2013;43(3):298-307. **37.** Nishimura JI, Kanakura Y, Ware RE, et al. Clinical course and flow cytometric analysis of paroxysmal nocturnal hemoglobinuria in the United States and Japan. *Medicine.* 2004;83(3):193-207. **38.** Hill A, Rother RP, Wang X, et al. Effect of eculizumab on haemolysis associated nitric oxide depletion, dyspnoea, and measures of pulmonary hypertension in patients with paroxysmal nocturnal haemoglobinuria. *Br J Haematol.* 2010;149(3):414-425. **39.** Hill A, Sapsford RJ, Scally A, et al. Under-recognized complications in patients with paroxysmal nocturnal haemoglobinuria: raised pulmonary pressure and reduced right ventricular function. *Br J Haematol.* 2012;158(3):409-414. **40.** Jang JH, Kim JS, Yoon SS, et al. Predictive factors of mortality in population of patients with paroxysmal nocturnal hemoglobinuria (PNH): results from a Korean PNH registry. *J Korean Med Sci.* 2016;31(2):214-221.

Please see Important Safety Information on pages 1 and 17-18 and accompanying full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections.

ULTOMIRIS® (ravulizumab-cwvz) injection for intravenous use 300 mg/3 mL vial

IMPORTANT SAFETY INFORMATION for ULTOMIRIS® (ravulizumab-cwvz) (cont'd)

CONTRAINDICATIONS

- Initiation in patients with unresolved serious *Neisseria meningitidis* infection.

WARNINGS AND PRECAUTIONS

Serious Meningococcal Infections

ULTOMIRIS, a complement inhibitor, increases a patient's susceptibility to serious, life-threatening, or fatal infections caused by meningococcal bacteria (septicemia and/or meningitis) in any serogroup, including non-groupable strains. Life-threatening and fatal meningococcal infections have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors.

Revaccinate patients in accordance with ACIP recommendations considering the duration of ULTOMIRIS therapy. Note that ACIP recommends an administration schedule in patients receiving complement inhibitors that differs from the administration schedule in the vaccine prescribing information. If urgent ULTOMIRIS therapy is indicated in a patient who is not up to date with meningococcal vaccines according to ACIP recommendations, provide antibacterial drug prophylaxis and administer meningococcal vaccines as soon as possible. Various durations and regimens of antibacterial drug prophylaxis have been considered, but the optimal durations and drug regimens for prophylaxis and their efficacy have not been studied in unvaccinated or vaccinated patients receiving complement inhibitors, including ULTOMIRIS. The benefits and risks of treatment with ULTOMIRIS, as well as those associated with antibacterial drug prophylaxis in unvaccinated or vaccinated patients, must be considered against the known risks for serious infections caused by *Neisseria meningitidis*.

Vaccination does not eliminate the risk of serious meningococcal infections, despite development of antibodies following vaccination.

Closely monitor patients for early signs and symptoms of meningococcal infection and evaluate patients immediately if infection is suspected. Inform patients of these signs and symptoms and instruct patients to seek immediate medical care if they occur. Promptly treat known infections. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early. Consider interruption of ULTOMIRIS in patients who are undergoing treatment for serious meningococcal infection depending on the risks of interrupting treatment in the disease being treated.

ULTOMIRIS and SOLIRIS REMS

Due to the risk of serious meningococcal infections, ULTOMIRIS is available only through a restricted program called ULTOMIRIS and SOLIRIS REMS.

Prescribers must enroll in the REMS, counsel patients about the risk of serious meningococcal infection, provide patients with the REMS educational materials, assess patient vaccination status for meningococcal vaccines (against serogroups A, C, W, Y, and B) and vaccinate if needed according to current ACIP recommendations two weeks prior to the first dose of ULTOMIRIS. Antibacterial drug prophylaxis must be prescribed if treatment must be started urgently, and the patient is not up to date with both meningococcal vaccines according to current ACIP recommendations at least two weeks prior to the first dose of ULTOMIRIS. Patients must receive counseling about the need to receive meningococcal vaccines and to take antibiotics as directed, signs and symptoms of meningococcal infection, and be instructed to carry the Patient Safety Card at all times during and for 8 months following ULTOMIRIS treatment.

Further information is available at www.UltSolREMS.com or 1-888-765-4747.

Other Infections

Serious infections with *Neisseria* species (other than *Neisseria meningitidis*), including disseminated gonococcal infections, have been reported.

ULTOMIRIS blocks terminal complement activation; therefore, patients may have increased susceptibility to infections, especially with encapsulated bacteria, such as infections caused by *Neisseria meningitidis* but also *Streptococcus pneumoniae*, *Haemophilus influenzae*, and to a lesser extent, *Neisseria gonorrhoeae*. Children treated with ULTOMIRIS may be at increased risk of developing serious infections due to *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib). Administer vaccinations for the prevention of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) infections according to ACIP recommendations. Patients receiving ULTOMIRIS are at increased risk for infections due to these organisms, even if they develop antibodies following vaccination.

Please see Important Safety Information on pages 1 and 17-18 and accompanying full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections.

ULTOMIRIS® (ravulizumab-cwvz) injection for intravenous use 300 mg/3 mL vial

IMPORTANT SAFETY INFORMATION for ULTOMIRIS® (ravulizumab-cwvz) (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Monitoring Disease Manifestations after ULTOMIRIS Discontinuation

After discontinuing treatment with ULTOMIRIS, closely monitor for signs and symptoms of hemolysis, identified by elevated LDH along with sudden decrease in PNH clone size or hemoglobin, or re-appearance of symptoms such as fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction. Monitor any patient who discontinues ULTOMIRIS for at least 16 weeks to detect hemolysis and other reactions. If signs and symptoms of hemolysis occur after discontinuation, including elevated LDH, consider restarting treatment with ULTOMIRIS.

Thromboembolic Event Management

The effect of withdrawal of anticoagulant therapy during treatment with ULTOMIRIS has not been established. Treatment should not alter anticoagulant management.

Infusion-Related Reactions

Administration of ULTOMIRIS may result in systemic infusion-related reactions, including anaphylaxis and hypersensitivity reactions. In clinical trials, infusion-related reactions occurred in approximately 1 to 7% of patients, including lower back pain, abdominal pain, muscle spasms, drop or elevation in blood pressure, rigors, limb discomfort, drug hypersensitivity (allergic reaction), and dysgeusia (bad taste). These reactions did not require discontinuation of ULTOMIRIS. If signs of cardiovascular instability or respiratory compromise occur, interrupt ULTOMIRIS and institute appropriate supportive measures.

ADVERSE REACTIONS

Adverse reactions reported in ≥10% or more of patients with PNH were upper respiratory tract infection and headache. Serious adverse reactions were reported in 15 (6.8%) patients receiving ULTOMIRIS. The serious adverse reactions in patients treated with ULTOMIRIS included hyperthermia and pyrexia. No serious adverse reaction was reported in more than 1 patient treated with ULTOMIRIS. One fatal case of sepsis was identified in a patient treated with ULTOMIRIS. In clinical studies, clinically relevant adverse reactions in 1% of adult patients include infusion-related reactions.

Adverse reactions reported in ≥10% of pediatric patients treated with ULTOMIRIS who were treatment-naïve vs. Eculizumab-experienced were anemia (20% vs. 25%), abdominal pain (0% vs. 38%), constipation (0% vs. 25%), pyrexia (20% vs. 13%), upper respiratory tract infection (20% vs. 75%), pain in extremity (0% vs. 25%), and headache (20% vs. 25%).

DRUG INTERACTIONS

Plasma Exchange, Plasmapheresis, and Intravenous Immunoglobulins

Concomitant use of ULTOMIRIS with plasma exchange (PE), plasmapheresis (PP), or intravenous immunoglobulin (IVIg) treatment can reduce serum ravulizumab concentrations and requires a supplemental dose of ULTOMIRIS.

Neonatal Fc Receptor Blockers

Concomitant use of ULTOMIRIS with neonatal Fc receptor (FcRn) blockers (e.g., efgartigimod) may lower systemic exposures and reduce effectiveness of ULTOMIRIS. Closely monitor for reduced effectiveness of ULTOMIRIS.

USE IN SPECIFIC POPULATIONS

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ULTOMIRIS during pregnancy. Healthcare providers and patients may call 1-833-793-0563 or go to www.UltomirisPregnancyStudy.com to enroll in or to obtain information about the registry.

To report SUSPECTED ADVERSE REACTIONS, contact Alexion Pharmaceuticals, Inc. at 1-844-259-6783 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see accompanying full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections.