Sample Appeal Letter for ULTOMIRIS® (ravulizumab-cwvz)
for Paroxysmal Nocturnal Hemoglobinuria (PNH)

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.

INDICATION

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

Subcutaneous Use in Adult Patients with PNH
Subcutaneous administration of ULTOMIRIS is not approved for use in pediatric patients.

SELECT IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

Life-threatening meningococcal infections/sepsis have occurred in patients treated with ULTOMIRIS. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early.

- **Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.**
- **Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of ULTOMIRIS, unless the risks of delaying ULTOMIRIS therapy outweigh the risk of developing a meningococcal infection. See *Warnings and Precautions* for additional guidance on the management of the risk of meningococcal infection.**
- **Vaccination reduces, but does not eliminate, the risk of meningococcal infections. Monitor patients for early signs of 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 REMS.

Please see Important Safety Information on pages 11 and 12 and the full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious meningococcal infections/sepsis.

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

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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

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[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 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. 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. Refer to "Treatment Rationale to Support Appeal" on pages 5-6.

If applicable, describe your patient's treatment goals and your rationale why a step-therapy through pegcetacoplan is not optimal for meeting these goals. Refer to "Treatment Rationale to Support Appeal" on pages 5-6.

In my medical opinion, ULTOMIRIS remains the most appropriate treatment for [Name of patient].

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

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

SAMPLE ONLY
Please copy onto your letterhead.

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]

Attachments
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 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:** Provide documentation of history of red blood cell/white blood cell transfusions [number of infusions, dates, as well as the units transfused].
- **Denial due to patient not meeting thrombotic risk (no clot or clone size is too small, no 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, MRI, CT, and/or PNH clone size (indicative of risk for thromboembolic events)].
- **Denial due to omission of necessary lab results:** Provide any appropriate or confirmatory lab values [evidence of LDH level ≥1.5 times the upper limit of normal, abnormal high sensitivity flow cytometry results, negative direct antiglobulin or Coombs' test, elevated reticulocytes, or decreased levels of serum haptoglobin].
- **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 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)].[2,3] According to the prescribing information, it took four to six weeks for pegcetacoplan to achieve steady-state serum concentrations following the first dose.[4] In my medical opinion, pegcetacoplan will not mitigate this acute crisis.
  - **Patient is under 18 years of age**
    [Name of patient] is [age] years old. Pegcetacoplan is not indicated for pediatric patients under age 18.[4]
  - **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 non-adherence 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.[4] 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.)

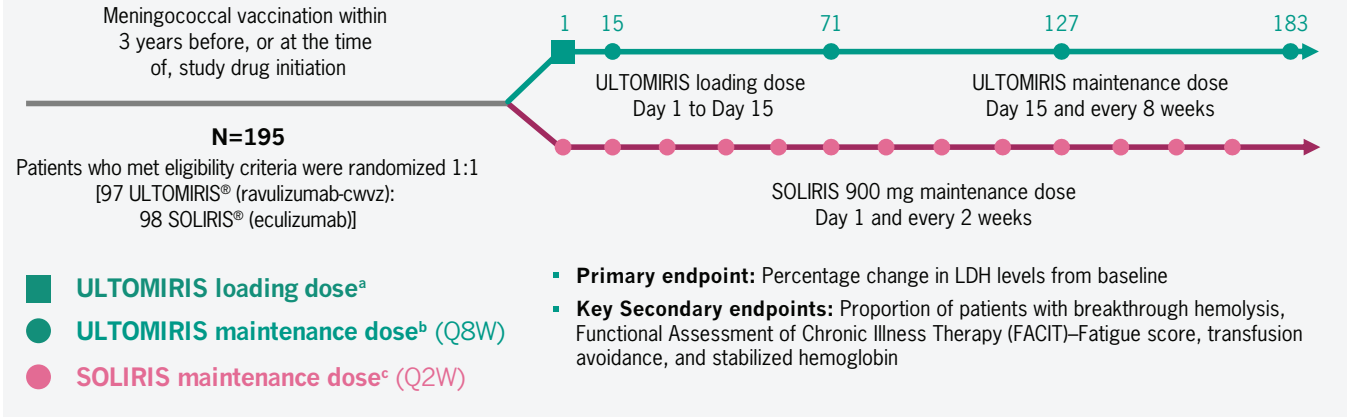
PEGASUS Study Design – Select Patient Inclusion Criteria
In my medical opinion, pegcetacoplan is not an appropriate step for my patient as they would not been included in the PEGASUS phase 3 clinical trial based on the following select relevant study inclusion criteria. [List specific reason(s) based on provided select 'PEGASUS Study – Select Patient Inclusion Criteria' on the next page][5,6]

- Patients with hemoglobin level <10.5 g/dl despite treatment with stable doses of eculizumab for ≥3 months prior to screening[5,6]
- Patients were required to have reticulocytes >1.0 × ULN[5,6]
- Participants were also required to have a body mass index <35.0 kg/m^2 and platelets >50×10^9/l at screening prior to study entry[5,6]

1 Treatment Rationale to Support Appeal (cont.)

Rationale for required use of ULTOMIRIS® (ravulizumab-cwvz)
Study 302: Phase 3, open-label, randomized, non-inferiority, active-controlled trial evaluating the efficacy and safety of ULTOMIRIS in 195 adult patients with PNH who were stable on SOLIRIS and received ULTOMIRIS (N=97) or SOLIRIS (N=98).[7]

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



[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 one 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[7]
- 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])[7]
- 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)[7]
- 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[7]
- 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 11 and 12 and the full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious meningococcal infections/sepsis.

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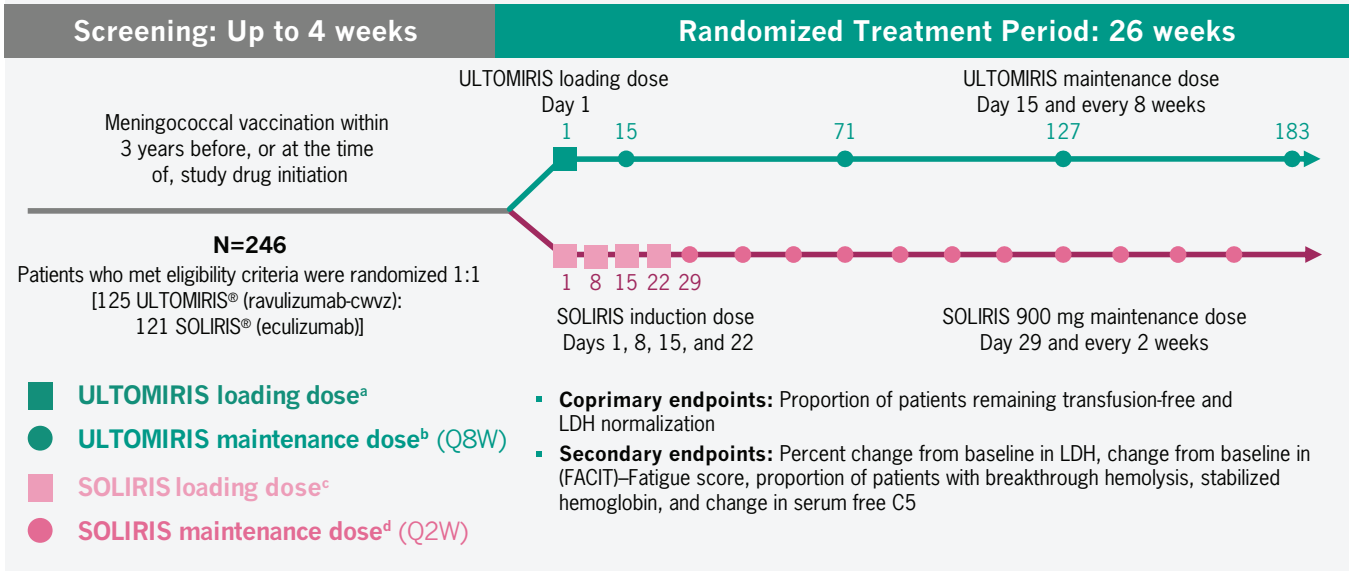
1 Treatment Rationale to Support Appeal (cont.)

Study 301: Phase 3, open-label, randomized, non-inferiority, active-controlled trial evaluating the efficacy and safety of ULTOMIRIS® (ravulizumab-cwvz) in 246 complement inhibitor-naïve adult patients with PNH who received ULTOMIRIS (N=125) or SOLIRIS (N=121).[8]

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



[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 FDA approved for treatment of PNH in adult and pediatric patients one 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[8]
- Proportions of patients with breakthrough hemolysis were 4.0% in the ULTOMIRIS group vs 10.7% in the SOLIRIS group (difference, −6.7% [95% CI: −14.21, 0.18]; P_{inf} <.0001)[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%[8]
- The adjusted prevalence of LDH normalization was 53.6% for the ULTOMIRIS group and 49.4% for the SOLIRIS group; the adjusted 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[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]

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1 Treatment Rationale to Support Appeal (cont.)

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].[7,8] 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 IVH, preventing thrombosis, reducing breakthrough hemolysis, decreasing end organ damage].[9-18]

- **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].[7,8] [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].[9-18]

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

ULTOMIRIS Prescribing Information, original denial letter, ULTOMIRIS Letter of Medical Necessity, ULTOMIRIS Access and Reimbursement Guide

References: 1. ULTOMIRIS. Prescribing information. Alexion Pharmaceuticals, Inc. **2.** Brodsky RA. Treatment and prognosis of paroxysmal nocturnal hemoglobinuria. UpToDate website. Updated December 3, 2021. Accessed February 14, 2022. https://www.uptodate.com/contents/treatment-and-prognosis-of-paroxysmal-nocturnal-hemoglobinuria **3.** Hill A, DeZern AE, Kinoshita T, Brodsky RA. Paroxysmal nocturnal haemoglobinuria. *Nat Rev Dis Primers*. 2017;3:17028. **4.** Empaveli prescribing information. Apellis Pharmaceuticals, Inc. **5.** Hillmen P, Szer J, Weitz I, et al. Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 2021;384(11):1028-1037. **6.** Hillmen P, Szer J, Weitz I, et al. Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 2021;384(11)(suppl):1028-1037. Accessed February 14, 2022. https://www.nejm.org/doi/suppl/10.1056/NEJMoa2029073/suppl_file/nejmoa2029073_appendix.pdf **7.** 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. **8.** 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. **9.** Hill A, Kelly RJ, Hillmen P. Thrombosis in paroxysmal nocturnal hemoglobinuria. *Blood*. 2013;121(25):4985-4996. **10.** De Latour RP, Mary JY, Salanoubat C, et al. Paroxysmal nocturnal hemoglobinuria: natural history of disease subcategories. *Blood*. 2008;112(8):3099-3106. **11.** 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. **12.** 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. **13.** Clark DA, Butler SA, Braren V, Hartman RC, Jenkins DE Jr. The kidneys in paroxysmal nocturnal hemoglobinuria. *Blood*. 1981;57(1):83-89. **14.** 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. **15.** 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. **16.** 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 May;149(3):414-425. **17.** 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. **18.** 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.

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INDICATION & IMPORTANT SAFETY INFORMATION FOR ULTOMIRIS® (ravulizumab-cwvz) (cont.)

INDICATION

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

Subcutaneous Use in Adult Patients with PNH

Subcutaneous administration of ULTOMIRIS is not approved for use in pediatric patients.

IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

Life-threatening meningococcal infections/sepsis have occurred in patients treated with ULTOMIRIS. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early.

- **Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.**
- **Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of ULTOMIRIS, unless the risks of delaying ULTOMIRIS therapy outweigh the risk of developing a meningococcal infection. See *Warnings and Precautions* for additional guidance on the management of the risk of meningococcal infection.**
- **Vaccination reduces, but does not eliminate, the risk of meningococcal infections. Monitor patients for early signs of 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 REMS.

CONTRAINDICATIONS

- Patients with unresolved *Neisseria meningitidis* infection.
- Patients who are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying ULTOMIRIS treatment outweigh the risks of developing a meningococcal infection.

WARNINGS AND PRECAUTIONS

Serious Meningococcal Infections

Life-threatening meningococcal infections have occurred in patients treated with ULTOMIRIS. The use of ULTOMIRIS increases a patient's susceptibility to serious meningococcal infections (septicemia and/or meningitis). Meningococcal disease due to any serogroup may occur.

Vaccinate or revaccinate for meningococcal disease according to the most current ACIP recommendations for patients with complement deficiencies. Immunize patients without history of meningococcal vaccination at least 2 weeks prior to the first dose of ULTOMIRIS. Patients who initiate ULTOMIRIS treatment less than 2 weeks after receiving meningococcal vaccine(s) must receive appropriate prophylactic antibiotics until 2 weeks after vaccination.

In clinical studies, 59 adult patients with PNH were treated with ULTOMIRIS less than 2 weeks after meningococcal vaccination. All of these patients received antibiotics for prophylaxis of meningococcal infection until at least 2 weeks after meningococcal vaccination. The benefits and risks of antibiotic prophylaxis for prevention of meningococcal infections in patients receiving ULTOMIRIS have not been established. In clinical studies with ULTOMIRIS, <1% of patients developed serious meningococcal infections/sepsis while receiving treatment with ULTOMIRIS. All were adult patients with PNH who had been vaccinated. These patients recovered while continuing treatment with ULTOMIRIS. Consider discontinuation of ULTOMIRIS in patients who are undergoing treatment for serious meningococcal infection.

ULTOMIRIS REMS

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

Under the ULTOMIRIS REMS, prescribers must enroll in the program. Prescribers must counsel patients about the risk of meningococcal infection/sepsis, provide the patients with the REMS educational materials, and ensure patients are vaccinated with meningococcal vaccines.

Additional information on the REMS requirements is available at www.ultomirisrems.com or 1-888-765-4747.

Please see Important Safety Information on pages 11 and 12 and the full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious meningococcal infections/sepsis.

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

US/ULT-P/0313 10/22

Other Infections
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 guidelines. If ULTOMIRIS is administered to patients with active systemic infections, monitor closely for worsening infection.

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
Intravenous or subcutaneous 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% of patients treated with ULTOMIRIS. These events included lower back pain, drop in blood pressure, elevation in blood pressure, limb discomfort, drug hypersensitivity (allergic reaction), dysgeusia (bad taste), and drowsiness. These reactions did not require discontinuation of ULTOMIRIS. If signs of cardiovascular instability or respiratory compromise occur, interrupt ULTOMIRIS infusion and institute appropriate supportive measures.

Injection Site Reactions- Subcutaneous administration
27% (23/84) of patients treated with subcutaneous administration of ULTOMIRIS experienced injection site reactions which included application site rash, device allergy, infusion site pain, infusion site reaction, injection site bruising, injection site erythema, injection site hematoma, injection site induration, injection site inflammation, injection site pain, injection site pruritus, injection site rash, injection site reaction, injection site swelling, injection site urticaria, medical device site bruise, medical device site erythema, medical device site hematoma, medical device site induration, medical device site pruritus, medical device site rash, and medical device site reaction.

Allergies to Acrylic Adhesives
The on-body injector of ULTOMIRIS uses acrylic adhesive. For patients with a known allergy to acrylic adhesive, use of this product may result in an allergic reaction. Premedication can be considered, and supportive measures should be instituted if signs of allergy appear.

ADVERSE REACTIONS

Adverse reactions reported in 5% or more of patients treated with ULTOMIRIS vs. Eculizumab was Upper respiratory tract infection (39% vs. 39%), Headache (32% vs. 26%), Diarrhea (9% vs. 5%), Nausea (9% vs. 9%), Pyrexia (7% vs. 8%), Pain in extremity (6% vs. 5%), Abdominal pain (6% vs. 7%), Dizziness (5% vs. 6%), Arthralgia (5% vs. 5%). 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% or more of pediatric patients treated with ULTOMIRIS who were treatment-naïve vs. Eculizumab-experienced was 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%), Headache (20% vs. 25%).

Adverse Reactions for Subcutaneous Administration of ULTOMIRIS
Most common adverse reactions (≥10%) with ULTOMIRIS subcutaneous administration via On Body Injector in adult patients with PNH were local injection site reactions, diarrhea, and headache.

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.

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ALEXION®
AstraZeneca Rare Disease