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

Sample Appeal Letter for ULTOMIRIS

for Atypical Hemolytic Uremic Syndrome (aHUS)

INDICATION & SELECT IMPORTANT SAFETY INFORMATION for ULTOMIRIS

INDICATION

ULTOMIRIS is indicated for the treatment of adult and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA).

Limitation of Use:
ULTOMIRIS is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

SELECT 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 10-11 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 atypical hemolytic uremic syndrome (aHUS), 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.

Table of Contents

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

Contact form: Connect with a Field Reimbursement Manager

[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 atypical hemolytic uremic syndrome (aHUS). In the letter referenced above, the denial reason was stated as follows: [insert reason for denial: eg, a requirement of a history of trial/failure of or intolerance to eculizumab, eculizumab-aagh, or eculizumab-aeeb therapy]. 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 and 7.

If applicable, describe your patient's treatment goals and your rationale why a step therapy through eculizumab, 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 or intolerance to eculizumab, eculizumab-aagh, or eculizumab-aeeb. Refer to "Treatment Rationale to Support Appeal" on pages 6 and 7.

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 6-9; 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 ravulizumab regimen].

Based on my assessment of their current clinical symptoms and labs, they require [insert recommendations for addressing patient's current therapeutic needs (eg, effective long-term control of aHUS drastic manifestations including: reduction of dialysis; maintenance of stable regimen; and more time between doses] 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 an aHUS 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 treatment options with aHUS. My patient has shared in the decision-making process regarding their aHUS therapy plan. Collectively, we have determined that ULTOMIRIS is the most clinically appropriate treatment choice for managing their aHUS at this time.

For the above reasons, I request that you approve ULTOMIRIS for the treatment of this patient.

3 ATTACHMENTS AND SUPPORTING DOCUMENTATION

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 phone 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 atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA). Limitation of use: ULTOMIRIS is not indicated for the treatment of patients with Shiga toxin *Escherichia coli* related hemolytic uremic syndrome (STEC-HUS).[1]
- **Denial due to underlying etiology:** Provide documentation to confirm diagnosis of aHUS in a patient with signs of TMA by ruling out thrombocytopenic purpura (TTP) and STEC-HUS.[2,3]
  - o Evidence of thrombocytopenia: Platelet count <150 x 10^9/L or >25% decrease from baseline.

  AND

  - o Evidence of microangiopathic hemolytic anemia: schistocytes and/or elevated LDH and/or decreased haptoglobin and/or decreased hemoglobin.

  AND one or more symptoms listed below

  - o Common symptoms: neurologic symptoms (confusion, seizures, stroke, and/or other cerebral abnormalities), renal impairment (elevated creatinine level, decreased eGFR, elevated blood pressure, and/or abnormal urinalysis), gastrointestinal symptoms (diarrhea ± blood, nausea/vomiting, abdominal pain, and/or gastroenteritis/pancreatitis). Other symptoms include cardiovascular symptoms (myocardial infarction, hypertension, arterial stenosis, and/or peripheral gangrene), pulmonary symptoms (dyspnea, pulmonary hemorrhage, and/or pulmonary edema), and visual symptoms (pain and blurred vision, retinal vessel occlusion, and/or ocular hemorrhage).

  AND

  - o Provide documentation for >5% ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity and Shiga toxin *Escherichia coli* test results.
- **Denial due to meningococcal vaccinations:** Provide documentation of initial series and/or most recent boosters for meningococcal vaccination (for serogroups A, C, W, Y and B). If vaccinations are pending approval of therapy, please include a scheduled date for patient to receive the vaccinations.[1]
- **Denial due to omission of necessary lab results:** Provide any appropriate or confirmatory lab values [platelet count <150 x 10^9/L or >25% decrease from baseline, presence of schistocytes, elevated LDH, decreased haptoglobin, decreased hemoglobin, serum creatinine ≥ ULN or required dialysis].[2]
- **Denial due to required step therapy:** Please see respective sections below for supporting statements against the use of step therapy through eculizumab, eculizumab-aagh, or eculizumab-aeeb:
  - o **Denial due to use of eculizumab:** In my medical opinion, eculizumab is not an appropriate step therapy for my patient based on the following relevant clinical criteria [below is a list of potential considerations why eculizumab 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].
    - The patient had a previous diagnosis of aHUS that met requirements for initiating eculizumab, was clinically stable on eculizumab, and achieved a complete TMA response as evidenced by [normalization of platelet count, normalization of LDH, ≥25% improvement in serum creatinine from baseline].[2,4]

1 Treatment Rationale to Support Appeal (cont'd)

- Switching to ULTOMIRIS reduces maintenance dosing frequency to 6 to 7 infusions per year in patients who weigh ≥20 kg, from 26 infusions per year with eculizumab in patients who weigh ≥10 kg. The patient is unable to comply with the maintenance treatment dosing interval of every 2 weeks for eculizumab because of [fill in reason for patient being unable to reach office for infusion (eg, lack of transportation, job scheduling, other personal obligations)]. Currently, the patient can maintain the dosing interval schedule of every [4 weeks (ie, for patients weighing 5 kg to <20 kg) or 8 weeks (ie, for patients weighing ≥20 kg to ≥100 kg)] for ULTOMIRIS.[1,4]
- ULTOMIRIS was engineered through the modification of eculizumab to result in an extended half-life with the same mechanism of action.[1,4]

o **Denial due to use of biosimilar [eculizumab-aagh or eculizumab-aeeb]:** In my medical opinion, [eculizumab-aagh or eculizumab-aeeb] is not an appropriate step therapy 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 with [eculizumab-aagh or eculizumab-aeeb]**

  The patient is currently being treated for aHUS with ULTOMIRIS. Based on my medical experience, a non-medical switch with [eculizumab-aagh or eculizumab-aeeb] could result in potential interrupted therapy due to treatment logistics (eg, biosimilar REMS requirements) and/or side effects. Since the patient is currently clinically stable on ULTOMIRIS as shown with [normalization of platelet count, normalization of LDH, ≥25% improvement in serum creatinine from baseline],[1,2] the patient and I have a strong preference to continue using ULTOMIRIS in treating [his/her/their] aHUS.

- **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 conditions]. Due to this [allergic reaction, intolerance, or incompatible medical conditions], it would be in the patient's best interest to continue using ULTOMIRIS as [he is/she is/they are] currently stable as shown [normalization of platelet count, normalization of LDH, ≥25% improvement in serum creatinine from baseline].[1,2]

- **Patient is not amendable to biweekly dosing regimen for [eculizumab-aagh or eculizumab-aeeb]**

  The patient is unable to comply with the maintenance treatment dosing interval of every 2 weeks in patients weighing ≥10 kg for [eculizumab-aagh[5] or eculizumab-aeeb[6]] because of [fill in reason for patient being unable to reach office for infusion (eg, lack of transportation, job scheduling, other personal obligations)]. Currently, the patient can maintain the dosing interval schedule of every [4 weeks (ie, for patients weighing 5 kg to <20 kg) or 8 weeks (ie, for patients weighing ≥20 kg to ≥100 kg)] for ULTOMIRIS.[1]

- **Real-world evidence**

  ULTOMIRIS has 5 years of real-world data.[1,7,8]

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

Health plans often require a 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.

ULTOMIRIS treatment of aHUS should be a minimum duration of 6 months. Due to heterogeneous nature of aHUS events and patient-specific risk factors, treatment duration beyond the initial 6 months should be individualized.[1]

- **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: complete TMA response defined as platelet count normalization, LDH normalization, 25% improvement in serum creatinine from baseline, hematologic normalization (normalization of both LDH and platelet count); improvement in eGFR from baseline; reduction or discontinuation of required dialysis treatments; patient-reported outcomes].[9,10] 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.

- **Denial due to change in policy-required step edit:**
  [Name of patient] was diagnosed with aHUS on [date] and has received ULTOMIRIS treatment since [date of first infusion]. [Name of patient] received authorization for ULTOMIRIS based on initial PA criteria. [He is/She is/They are] currently responding positively to treatment with ULTOMIRIS as demonstrated by [list specific measures such as: complete TMA response defined as platelet count normalization, LDH normalization, 25% improvement in serum creatinine, hematologic normalization (normalization of both LDH and platelet count); improvement in eGFR from baseline; reduction or discontinuation of required dialysis treatments; patient-reported outcomes].[9,10] [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.

2 Optional Medical History

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

- Lab results confirming diagnosis of aHUS – evidence of TMA including[2]:
  - Platelet count <150 x 10^9/L or >25% decrease from baseline **AND**
  - Schistocytes **AND/OR**
  - Elevated serum LDH **AND/OR**
  - Decreased hemoglobin **AND/OR**
  - Decreased haptoglobin **AND**
  - Evidence of involvement of at least 1 organ system such as renal involvement as evidence by serum creatinine
- Diagnosis of thrombocytopenic purpura (TTP) (≤5% ADAMTS13 activity) has been excluded[2]
- Absence of Shiga toxin-producing *Escherichia coli* infection[2]

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, or 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

eGFR, estimated glomerular filtration rate; **LDH,** lactate dehydrogenase; **REMS,** risk evaluation and mitigation strategy; **ULN,** upper limit of normal; **US,** United States.

References: 1. ULTOMIRIS. Prescribing Information. Alexion Pharmaceuticals, Inc. **2.** Laurence J, et al. *Clin Adv Hematol Oncol*. 2016;14(11)(suppl 11):2-15. **3.** Azoulay E, et al. *Chest*. 2017;152:424-434. **4.** SOLIRIS. Prescribing Information. Alexion Pharmaceuticals, Inc. **5.** EPYSQLI. Prescribing Information. Samsung Bioepis Co., Ltd. **6.** BKEMV. Prescribing Information. Amgen Inc. **7.** Barbour T, et al. *Kidney Int Rep*. 2021;6(6):1603-1613. **8.** Alexion Pharmaceuticals, Inc. Alexion receives FDA approval for ULTOMIRIS (ravulizumab-cwvz) for atypical hemolytic uremic syndrome (aHUS). Updated October 18, 2019. Accessed December 5, 2024. https://media.alexion.com/news-releases/news-release-details/alexion-receives-fda-approval-ultomirisr-ravulizumab-cwvz **9.** Rondeau E, et al. *Kidney Int*. 2020;97(6):1287-1296. **10.** Ariceta G, et al. *Kidney Int*. 2021;100(1):225-237.

SELECT IMPORTANT SAFETY INFORMATION for ULTOMIRIS (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.

SELECT IMPORTANT SAFETY INFORMATION for ULTOMIRIS (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Monitoring Disease Manifestations after ULTOMIRIS Discontinuation

ULTOMIRIS treatment of aHUS should be a minimum duration of 6 months. Due to heterogeneous nature of aHUS events and patient-specific risk factors, treatment duration beyond the initial 6 months should be individualized. There are no specific data on ULTOMIRIS discontinuation. After discontinuing treatment with ULTOMIRIS, patients should be monitored for clinical symptoms and laboratory signs of TMA complications for at least 12 months. TMA complications post-discontinuation can be identified if any of the following is observed: Clinical symptoms of TMA include changes in mental status, seizures, angina, dyspnea, thrombosis or increasing blood pressure. In addition, at least two of the following laboratory signs observed concurrently and results should be confirmed by a second measurement 28 days apart with no interruption: a decrease in platelet count of 25% or more as compared to either baseline or to peak platelet count during ULTOMIRIS treatment; an increase in serum creatinine of 25% or more as compared to baseline or to nadir during ULTOMIRIS treatment; or, an increase in serum LDH of 25% or more as compared to baseline or to nadir during ULTOMIRIS treatment. If TMA complications occur after discontinuation, consider reinitiation of ULTOMIRIS treatment or appropriate organ-specific supportive measures.

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

Most common adverse reactions in patients with aHUS (incidence ≥20%) were upper respiratory tract infection, diarrhea, nausea, vomiting, headache, hypertension and pyrexia. Serious adverse reactions were reported in 42 (57%) patients with aHUS receiving ULTOMIRIS. The most frequent serious adverse reactions reported in more than 2 patients (2.7%) treated with ULTOMIRIS were hypertension, pneumonia and abdominal pain.

Adverse reactions reported in ≥20% of pediatric patients treated with ULTOMIRIS were diarrhea, constipation, vomiting, pyrexia, upper respiratory tract infection, decreased vitamin D, headache, cough, rash, and hypertension.

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.

ALEXION® AstraZeneca Rare Disease