Sample Letter of Medical Necessity for ULTOMIRIS® (ravulizumab-cwvz) in Atypical Hemolytic Uremic Syndrome (atypical-HUS)

Payers may request a letter of medical necessity to support coverage of ULTOMIRIS. The letter should explain why the drug is medically necessary for the specific patient and may include supporting documentation (eg, medical records, peer-reviewed literature, Prescribing Information, clinical treatment history, etc). The letter may be submitted as part of a prior authorization (PA) request, with the claim form, or in response to a payer's request for additional documentation. The letter should include patient-specific information, be on the prescriber's letterhead, be signed by the prescriber, and be submitted to a payer to support a PA request or claim for ULTOMIRIS.

This sample letter of medical necessity is provided for informational purposes only and is not based on 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 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).

Subcutaneous Use in Adult Patients with aHUS
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.

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.

Please see Important Safety Information on pages 1 and 4 and the accompanying full Prescribing Information for ULTOMIRIS® (ravulizumab-cwvz), including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.

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

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[First Name Last Name], [Credentials]
12345 West Main Street
City Name, FL 33223
(888) 555-5555

SAMPLE ONLY

Please copy onto your letterhead.

[Date]
[Contact Name] [Title]
[Name of Health Insurance Company]
[Address] [City, State Zip Code]
Insured: [Name]; Policy Number: [Number]; Group Number: [Number]
Date(s) of service: [Date(s)]

Dear [Contact Name]:

I am writing on behalf of my patient, [First Name] [Last Name], to request that [name of health insurance company] approve coverage and appropriate reimbursement associated with [Mr/Ms/Mrs/other title] [Last Name]'s treatment with ULTOMIRIS® (ravulizumab-cwvz). ULTOMIRIS is indicated for the treatment of adults and pediatric patients 1 month of age and older with atypical hemolytic uremic syndrome (atypical-HUS) 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).

Patient History and Diagnosis
[Name of patient] is a[n] [age]-year-old [male/female] born [MM-DD-YEAR] who requires treatment with ULTOMIRIS after being diagnosed with atypical-HUS on [date of diagnosis MM-DD-YEAR].

1 **For C5 Treatment–Naïve Patients (reference page 3 for examples):**

[Provide a brief description of the patient's atypical-HUS symptoms and historical management, including any patient-specific clinical scenarios.] Please delete section if not applicable to your patient.

2 **For C5-Treated Patients Transitioning to ULTOMIRIS (reference page 3 for examples):**

[Provide a brief description of the patient's atypical-HUS symptoms and previous treatments for atypical-HUS, including any patient-specific clinical scenarios.] Please delete section if not applicable to your patient.

In my medical opinion, ULTOMIRIS is the most appropriate treatment for [name of patient]'s atypical-HUS based on the clinical efficacy and safety data.

Dosing[1]

For patients with atypical-HUS, the recommended dosing regimen for ULTOMIRIS includes a weight-based loading dose. Maintenance dosing starts 2 weeks after the initial loading dose and then occurs once every 4 weeks for patients 5 to <20 kg or every 8 weeks for patients >20 kg.

Patients 5 to <10 kg 600 mg loading dose; 300 mg maintenance dose (every 4 weeks)
Patients 10 to <20 kg 600 mg loading dose; 600 mg maintenance dose (every 4 weeks)
Patients 20 to <30 kg 900 mg loading dose; 2,100 mg maintenance dose (every 8 weeks)
Patients 30 to <40 kg 1,200 mg loading dose; 2,700 mg maintenance dose (every 8 weeks)
Patients 40 to <60 kg 2,400 mg loading dose; 3,000 mg maintenance dose (every 8 weeks)
Patients 60 to <100 kg 2,700 mg loading dose; 3,300 mg maintenance dose (every 8 weeks)
Patients ≥100 kg 3,000 mg loading dose; 3,600 mg maintenance dose (every 8 weeks)

Based on the above facts, I am confident you will agree that ULTOMIRIS is indicated and medically necessary for the treatment of atypical-HUS in this patient. If you have any further questions, please feel free to call me at [prescriber's telephone number] to discuss. Thank you in advance for your immediate attention to this request.

Sincerely,

[Prescriber's name], [Credentials]
[Prescriber's practice name] [Phone number]
Enclosures [Paper copy of original claim form, supporting clinical documentation, Prescribing Information, FDA approval letter for ULTOMIRIS in atypical-HUS, invoice, etc]

Please copy language above the line for sample letter.

Please see Important Safety Information on pages 1 and 4 and the accompanying full Prescribing Information for ULTOMIRIS® (ravulizumab-cwvz), including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.

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1 C5 TREATMENT FOR NAÏVE PATIENTS MAY INCLUDE:

- Clinical notes/laboratory reports with evidence of microangiopathic hemolytic anemia, acute kidney injury, and thrombocytopenia
- Platelet counts (note, only ≤150 x 10^9/L studied in clinical trial population)
- Evidence of hemolysis, including elevated LDH levels
- Elevated serum creatinine levels and renal function, as measured by eGFR
- Dialysis history, if any
- Daily TMA intervention rate, including interventions with plasma exchange, plasma infusion, and/or dialysis
- ADAMTS13 activity level results (note, only ≥5% studied in the clinical trial population)
- Negative test result for STEC-HUS
- Contraindications, if any, to any agents used in the treatment of atypical-HUS
- Meningococcal vaccinations: Provide documentation of initial series and/or most recent booster(s) for meningococcal vaccinations at least 2 weeks prior to the first proposed treatment with ULTOMIRIS (ravulizumab-cwvz)
- If urgent ULTOMIRIS (ravulizumab-cwvz) therapy is indicated in an unvaccinated patient, administer meningococcal vaccine(s) as soon as possible and provide patients with 2 weeks of antibacterial drug prophylaxis[1]
- Genetic test results, if available, and supportive of diagnosis. Please note, genetic testing is not required for diagnosis of atypical-HUS

2 C5-TREATED PATIENTS TRANSITIONING TO ULTOMIRIS:

- The patient had a previous diagnosis of atypical-HUS that met requirements for initiating SOLIRIS (eculizumab) and has had a beneficial response as evidenced by [reduction of LDH, improved platelet count, improved renal function]
- Switching to ULTOMIRIS reduces maintenance dosing frequency to 6 to 7 infusions per year for adult patients or 13 infusions per year for pediatric patients, from 26 infusions per year with SOLIRIS (eculizumab)[1,2]
- ULTOMIRIS has a half-life that is ~4x longer than SOLIRIS (eculizumab)[1,2]
- The patient will not receive ULTOMIRIS concomitantly with other complement inhibitors [eg, SOLIRIS (eculizumab)]

Please copy language above the line for sample letter.

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References: **1.** ULTOMIRIS. Prescribing information. Alexion Pharmaceuticals, Inc. **2.** SOLIRIS. Prescribing information. Alexion Pharmaceuticals, Inc.

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SELECT IMPORTANT SAFETY INFORMATION (cont.)

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.

The benefits and risks of antibiotic prophylaxis for prevention of meningococcal infections in patients receiving ULTOMIRIS have not been established. 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.

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
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
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

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. In clinical studies, clinically relevant adverse reactions in <10% of patients include viral tonsillitis in adults and viral infection in pediatric patients and in 3% of adult patients include infusion-related reactions.

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