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 & 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)*].

CONTRAINDICATIONS

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

Please see Important Safety Information on pages 1 and 4 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

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

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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 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 eculizumab[1,2]
- ULTOMIRIS has a half-life that is ~4x longer than eculizumab[1,2]
- The patient will not receive ULTOMIRIS concomitantly with other complement inhibitors [eg, eculizumab]

Please copy language above the line for sample letter.

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

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SELECT IMPORTANT SAFETY INFORMATION for ULTOMIRIS® (ravulizumab-cwvz) (cont.)

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.

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.

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ALEXION®
AstraZeneca Rare Disease