SAMPLE APPEAL LETTER FOR ULTOMIRIS® (ravulizumab-cwvz)

In Adult Patients Who Have Anti-Aquaporin-4 (AQP4) Antibody-Positive Neuromyelitis Optica Spectrum Disorder (NMOSD)

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 anti-aquaporin-4 (anti-AQP4) antibody-positive neuromyelitis optica spectrum disorder (NMOSD), 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 patients with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody positive.

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 page 1 and pages 9 and 10 and the 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

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, as well as 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
- **If the denial is due to step therapy protocols, emphasize specific reasons for exception to treatment. Reasons could include:**
  1. Contraindications to treatment
  2. Treatment could be ineffective due to clinical characteristics of patient
  3. Patient has tried and failed required treatment while on a previous health benefit plan
  4. Medication is not in the best interest of the patient based on medical necessity
  5. Patient is already stable on current treatment and should not disrupt continuity of care by switching to required step therapy

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

Our dedicated Field Reimbursement Managers (FRMs) can work with you. In the event of a PA denial, FRMs can provide you or your office staff with educational support and guidance. FRMs can help with:

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

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

SAMPLE ONLY
PLEASE COPY ONTO YOUR LETTERHEAD.

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

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

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

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

Dear [Contact Name],

I am writing to appeal the coverage denial for [Patient Name]'s treatment with ULTOMIRIS® (ravulizumab-cwvz) for anti-AQP4 antibody-positive neuromyelitis optica spectrum disorder (NMOSD). In the letter referenced above, you stated that the reason(s) for denial was/were [insert reason(s) for denial]. This letter provides information about my patient's medical history and my treatment rationale.

1 **REASON(S) FOR DENIAL AND TREATMENT RATIONALE (Refer to "Treatment Rationale to Support Appeal" and "Key Resources Available to You")**

[In the appeal letter, you need to address every denial reason(s) stated in the denial letter from the insurance plan. Clearly explain why the reason(s) stated by the insurance plan as a cause for denial of coverage does/do not preclude use of ULTOMIRIS. During the appeal process, it is generally not helpful to provide additional information beyond the specific denial reasons.]

In my medical opinion, ULTOMIRIS remains the most appropriate treatment for [Patient Name]. The stated reason(s) for denial was/were [insert each denial reason and address each reason point by point and provide any laboratory results if applicable].

2 **SUMMARY AND OPTIONAL MEDICAL HISTORY (Refer to "Optional Medical History")**

As stated in my initial authorization request, [Patient Name] presented with [insert specific clinical presentations and treatments for anti-AQP4 antibody-positive NMOSD, including any relevant patient-specific clinical scenarios demonstrating serious medical need]. 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.
[Provider Name]
[Provider Identification Number]
[Provider Practice Name]
[Provider Phone Number]
[Provider Fax Number]
[Provider Email]

Enclosures
[At the bottom of your letter, list the items you have enclosed, such as the original denial letter and ULTOMIRIS Full Prescribing Information. Be sure to include every article that you referenced or any new documentation.]

1 TREATMENT RATIONALE TO SUPPORT APPEAL

Below are some common reasons your patient's PA, precertification, or reauthorization request may be denied. In your appeal letter, ensure that each reason for denial is addressed by sharing your medical expertise on why the requirement is satisfied or should not apply in your patient's individual case. Be sure to attach the supporting references and any additional documentation in your reply.

- **Denial due to indication:** ULTOMIRIS is indicated for the treatment of adult patients with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (anti-AQP4) antibody-positive
- **Denial due to anti-AQP4 antibody test:** Evidence of a positive serological test for AQP4 antibodies [include laboratory results and date] and any other context you consider relevant around this laboratory result
- **Denial due to previous failed treatments:** Upon diagnosis with anti-AQP4 antibody-positive NMOSD, [Patient Name] was treated with [list treatments and associated dates (when available), along with the respective clinical responses here]. My rationale for treatment with ULTOMIRIS at this time is [include rationale here]
- **Denial due to the absence of core clinical characteristics:** [Patient Name] has a past medical history of [Choose one or more of the following:
  - Optic neuritis
  - Acute myelitis
  - Area postrema syndrome (episode of otherwise unexplained hiccups or nausea and vomiting)
  - Acute brainstem syndrome
  - Symptomatic narcolepsy or acute diencephalic clinical syndrome with anti-AQP4 antibody-positive NMOSD–typical diencephalic magnetic resonance imaging (MRI) lesions
  - Symptomatic cerebral syndrome with anti-AQP4 antibody-positive NMOSD–typical brain lesions and pertinent negative findings for other diagnoses such as multiple sclerosis, sarcoidosis, or neoplasm]
- **Denial due to insufficient history of relapses:** [Include detailed relapse history]. The ULTOMIRIS pivotal study, CHAMPION-NMOSD, required patients to have a history of at least one relapse in the past 12 months[1]
- **Denial due to Expanded Disability Status Scale (EDSS) score*:** [Include documentation of current score ≤7 (ie, presence of at least limited ambulation with aid) on the EDSS, including case notes and other clinical impressions.]
  - An EDSS score of ≤7 was assessed in the CHAMPION-NMOSD study[1]
  - ULTOMIRIS is approved for the treatment of adult patients with anti-AQP4 antibody-positive NMOSD[1]
- **Denial due to the absence of immunosuppressive therapy (IST) use:** [Patient Name] has tried and failed [list treatment names]. [He/she] has not shown adequate response due to [insert rationale and list specific reasons]. In the CHAMPION-NMOSD study, ~52% of patients were not on an IST at baseline[2†]
- **Denial due to the absence of corticosteroid use:** In my medical opinion, [list treatment names] is not an appropriate step for my patient due to [his/her] history of [describe relevant medical history which may include the following (not all inclusive):
  - Cardiometabolic disease.] Corticosteroids can induce hyperglycemia, hypertension, and weight gain. These effects can increase the risk of developing chronic conditions such as diabetes and cardiovascular disease[3]
  - Musculoskeletal disorder.] Corticosteroids can lead to muscle weakness and osteoporosis, affecting the musculoskeletal system's strength and bone density. These effects may increase the risk of fractures and impair physical function[3,4]
  - History of deteriorating vision.] Corticosteroids can increase the risk of developing cataracts and glaucoma, potentially leading to changes in vision or loss of sight. Prolonged use may also elevate intraocular pressure, requiring regular eye examinations to monitor and manage these effects[5]
  - Susceptible to infections.] Use of corticosteroids can decrease resistance and impair the ability to localize infections, potentially involving various pathogens (viral, bacterial, fungal, protozoan, or helminthic) in any body location, alone or with other immunosuppressive agents[5]

*EDSS score is based on a scale of 0 (no disability) to 10 (death).[2]
†There was a requirement for stable dosing until week 106 of study for the 48% of patients on an IST at baseline.[1,2]

- Gastrointestinal disorders.] Corticosteroids should be used with caution in active or latent peptic ulcers, diverticulitis, fresh intestinal anastomoses, and nonspecific ulcerative colitis, since they may increase the risk of a perforation[5]

- **Denial due to the absence of inebilizumab use:**
  - In my medical opinion, inebilizumab is not appropriate for my patient due to [his/her] history of [describe relevant medical history which may include the following (not all inclusive)[6]:
    - History of hepatitis B infections.] This condition is listed in the inebilizumab prescribing information as a warning and precaution in Section 5.2 under "Infections"
    - Progressive multifocal leukoencephalopathy (PML).] This condition is listed in the inebilizumab prescribing information as a warning and precaution in Section 5.2 under "Infections"
    - Tuberculosis.] This condition is listed in the inebilizumab prescribing information as a warning and precaution in Section 5.2 under "Infections"
    - Hypogammaglobulinemia.] This condition is listed in the inebilizumab prescribing information as a warning and precaution in Section 5.3 under "Reduction in Immunoglobulins." Prescribers should consider discontinuing inebilizumab if a patient with low immunoglobulin G or M develops serious opportunistic or recurrent infections, or requires IV immunoglobulins for prolonged deficiency
  - **N-MOmentum study design—select patient exclusion criteria[7]:**
    - Patients receiving alemtuzumab, total lymphoid irradiation, bone marrow transplant, or T-cell vaccination therapy
    - Patients who have received rituximab or any experimental B-cell–depleting agent within 6 months prior to treatment, unless their B-cell counts are above the lower limit of normal (LLN)
    - Patients with chronic active hepatitis B and/or hepatitis C
    - Pregnant or lactating women
    - Patients with a history of alcohol, drug, or chemical abuse within 1 year prior to study
    - Patients with a known history of a primary immunodeficiency (congenital or acquired) or an underlying condition such as human immunodeficiency virus (HIV) infection

- **Denial due to the absence of satralizumab use:**
  - In my medical opinion, satralizumab is not appropriate for my patient due to [his/her] history of [describe relevant medical history which may include the following (not all inclusive)[8]:
    - Hepatitis B infection.] This condition is listed in the satralizumab prescribing information as a warning and precaution in Section 5.1 under "Infections"
    - Tuberculosis.] This condition is listed in the satralizumab prescribing information as a warning and precaution in Section 5.1 under "Infections"
    - Liver enzymes elevation.] Mild and moderate elevations of liver enzymes were observed in patients treated with satralizumab at a higher incidence than placebo and is listed in the prescribing information as a warning and precaution in Section 5.2 under "Elevated Liver Enzymes"
    - Neutropenia.] Decreases in neutrophil counts were observed in patients treated with satralizumab at a higher incidence than placebo and is listed in the prescribing information as a warning and precaution in Section 5.3 under "Decreased Neutrophil Counts"
  - **SAkuraStar study design—select patient exclusion criteria[9]:**
    - Patients previously treated with IL-6 inhibitors (eg, tocilizumab), alemtuzumab, total body irradiation, or bone marrow transplantation
    - Pregnant or lactating women
    - Patients with evidence of other demyelinating diseases or Progressive Multifocal Leukoencephalopathy
    - Patients with uncontrolled diseases were excluded from trials, including those related to the nervous system, cardiovascular, hematologic, respiratory, muscular, endocrine, renal, urologic, digestive systems, or severe immunodeficiency
    - Patients with chronic active hepatitis B or C
    - Patients with active tuberculosis or receiving chemoprophylaxis for latent tuberculosis

  - Patients with an active interstitial lung disease, history of diverticulitis, or history of severe allergic reactions to biologic agents
  - Patients with a history of malignancy within the last 5 years, except for excised or cured basal cell and squamous cell skin carcinomas, or in situ cervical carcinoma

- **Denial due to the absence of rituximab use:**
  - In my medical opinion, rituximab is not appropriate for my patient due to [his/her] history of [describe relevant medical history which may include the following (not all inclusive)[10]:
    - Mucocutaneous reactions.] This condition is listed in the rituximab prescribing information as a warning and precaution in section 5.2 under "Severe Mucocutaneous Reactions"
    - Hepatitis B Reactivation.] This condition is listed in the rituximab prescribing information as a warning and precaution in section 5.3 under "Hepatitis B Virus (HBV) Reactivation"
    - Progressive Multifocal Leukoencephalopathy.] This condition is listed in the rituximab prescribing information as a warning and precaution in section 5.4 under "Progressive Multifocal Leukoencephalopathy (PML)"
    - Tumor Lysis Syndrome.] This condition is listed in the rituximab prescribing information as a warning and precaution in section 5.5 under "Tumor Lysis Syndrome (TLS)"
    - Heart issues (eg, angina, myocardial infarction, heart arrhythmia, etc).] This condition is listed in the rituximab prescribing information as a warning and precaution in Section 5.7 under "Cardiovascular Adverse Reactions"
    - Renal failure or insufficiencies.] This condition is listed in the rituximab prescribing information as a warning and precaution in Section 5.8 under "Renal Toxicity"
    - Bowel obstruction and perforation.] Abdominal pain, bowel obstruction, and perforation may occur in patients receiving rituximab in combination with chemotherapy and is listed in the rituximab prescribing information as a warning and precaution in section 5.9 under "Bowel Obstruction and Perforation"
    - Immunization.] The safety of immunization with live viral vaccines following rituximab therapy has been studied and vaccination with live virus vaccines is not recommended before or during treatment as a warning and precaution in Section 5.10 under "Immunization"
    - Embryo-Fetal Toxicity.] Rituximab can cause fetal harm due to B-cell lymphocytopenia in infants exposed to rituximab in-utero as a warning and precaution in Section 5.11 under "Embryo-Fetal Toxicity"
    - Cytopenias and/or hypogammaglobulinemia.] This condition is listed in the rituximab prescribing information as a warning and precaution in Section 5.6 under "Infections," and Section 6.1 under "Cytopenias and hypogammaglobulinemia"

- **Denial due to the absence of eculizumab use:**
  - The patient had a previous diagnosis of NMOSD that met requirements for initiating eculizumab, was clinically stable on eculizumab, and has had a beneficial response (ie, time to first adjudicated relapse)[1,11]
  - Switching to ULTOMIRIS reduces maintenance dosing frequency to 6 to 7 infusions per year 2 weeks after the loading dose, from 26 maintenance infusions per year with eculizumab[1,11]
  - ULTOMIRIS was engineered through the modification of eculizumab to result in an extended half-life with the same mechanism of action[1,11]
  - The annualized cost of treatment is expected to be reduced by ~25% to 37% with ULTOMIRIS compared with eculizumab based on wholesale acquisition cost (WAC)[1,11,12]

- **Denial due to required use of SOLIRIS® (eculizumab) biosimilar [eculizumab-aagh or eculizumab-aeeb]*:** In my medical opinion, [eculizumab-aagh or eculizumab-aeeb] is not an appropriate step for my patient based on the following relevant clinical criteria [below is a list of potential considerations why eculizumab-aagh or eculizumab-aeeb may not be appropriate for your patient given their case or specific clinical presentation. One or more of these reasons may apply to your patient's individual case]:
  - Non-medical switching
    - [Name of patient] is currently being treated for NMOSD with ULTOMIRIS. Based on my medical experience, a non-medical switch could result in potential interrupted therapy due to treatment logistics, side effects, and medication abandonment by the patient. Since [Name of patient] is currently stable on ULTOMIRIS as shown with clinical efficacy by a lack of relapse,[1,13] [Name of patient] and I have a strong preference to continue using ULTOMIRIS in treating [Name of patient]'s NMOSD
  - Patient is allergic to/intolerant of excipients present in [eculizumab-aagh or eculizumab-aeeb]
    - [Name of patient] is unable to take [eculizumab-aagh or eculizumab-aeeb] due to a[n] [allergic reaction or intolerance to trehalose in eculizumab-aagh or sorbitol, edetate disodium (EDTA), and/or sodium hydroxide in eculizumab-aeeb].[14,15] Due to this [allergic reaction or intolerance], it would be in the patient's best interest to continue using ULTOMIRIS as [he/she/they] [is/are] currently stable as shown by a lack of relapse[13]
  - Patient is not amendable to a biweekly dosing regimen for [eculizumab-aagh or eculizumab-aeeb]
    - [Name of patient] is unable to comply with the maintenance treatment dosing interval of every 2 weeks for [eculizumab-aagh or eculizumab-aeeb][14,15] because of [fill in reason for patient being unable to reach office for infusion (eg, lack of transportation, job scheduling, other personal obligations)]. Currently, [Name of patient] can maintain the dosing interval schedule of every [8 weeks, starting 2 weeks after the initial loading dose] for ULTOMIRIS[1]
  - [Eculizumab-aagh or eculizumab-aeeb] lacks real-world evidence
    - As [eculizumab-aagh or eculizumab-aeeb][16,17] was recently approved in 2024 for the treatment of aHUS and PNH, [eculizumab-aagh or eculizumab-aeeb] lacks real-world evidence for its use in all indications. [Name of patient] and I prefer to use a therapy, such as ULTOMIRIS, with real-world evidence through 6 years of approved use across multiple indications[1,17]
- **Denial due to meningococcal vaccinations:** Provide documentation of completing or updating the meningococcal vaccines for serogroups A, C, W, Y, and B at least 2 weeks prior to the first proposed treatment with ULTOMIRIS. If the patient was not vaccinated, provide documentation of antibacterial drug prophylaxis[1]

aHUS, atypical hemolytic-uremic syndrome; FDA, Food and Drug Administration; PNH, paroxysmal nocturnal hemoglobinuria.

*Eculizumab-aagh and eculizumab-aeeb are currently FDA approved for aHUS and PNH and would be considered off-label for the use of NMOSD.[15,16]

2 OPTIONAL MEDICAL HISTORY

- [Patient Name] is a [n] [age]-year-old [male/female] born on [MM/DD/YYYY] who requires treatment with ULTOMIRIS after being diagnosed with anti-AQP4 antibody-positive NMOSD on [date of diagnosis MM/DD/YYYY]
- **Current symptoms:** Examples such as respiratory dysfunction or failure, loss of bowel/bladder function, sensory and motor disability, severe weakness and impaired mobility, paralysis (paraparesis to paraplegia), and/or optic neuritis leading to pain in eye and loss of visual acuity[18-20]
  - It may be helpful to highlight in particular your patient's severity of disease based on your medical opinion and disease progression (eg, history of relapses)
- Documentation that the patient has had an inadequate response to sufficient trial therapies or has a contraindication to these medications before use of ULTOMIRIS is permitted, such as corticosteroids, immunosuppressive therapy (IST), inebilizumab, satralizumab, and/or rituximab in order to meet the plan's medical policy; pre-certification; or PA criteria
- Documentation of your clinical rationale to initiate ULTOMIRIS for this patient, such as contraindications to other therapies, clinical presentation, recent medical history, or visits related to NMOSD, etc
- Documentation of current medications for existing comorbidities that could lead to drug-drug interactions[1]
- Documentation of clinical stability and beneficial response of eculizumab as evidenced by [change from baseline in EDSS score, reduction in relapses][1,11]
- Documentation of reduction in relapses and change in EDSS score from baseline[1,2]

3 KEY RESOURCES AVAILABLE TO YOU

- Connect with an FRM—FRMs provide education and support to HCP offices to facilitate patient access to their prescribed Alexion medications
- The Compendium of Neuromyelitis Optica Spectrum Disorder (NMOSD) References for ULTOMIRIS provides information about specific scientific data and publications that may provide additional evidence for your appeal letter
- The Preparing for a Peer-to-Peer Medical Review resource provides education and support for HCPs, HCP offices, and infusion centers about using a peer-to-peer review as a potential next step before submitting a formal appeal

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

HCP, healthcare provider.

IMPORTANT SAFETY INFORMATION (CONTINUED)

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*. Patients receiving ULTOMIRIS are at increased risk for infections due to these organisms, even if they develop antibodies following vaccination.

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS (CONTINUED)

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 adult patients with NMOSD (incidence ≥10%) were COVID-19, headache, back pain, arthralgia, and urinary tract infection. Serious adverse reactions were reported in 8 (13.8%) patients with NMOSD receiving ULTOMIRIS.

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

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