A COMPENDIUM OF NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD) REFERENCES FOR ULTOMIRIS® (ravulizumab-cwvz)

When completing a prior authorization, precertification, reauthorization, or appeal request for ULTOMIRIS in the treatment of adults with anti-aquaporin-4 (AQP4) antibody-positive NMOSD, insurers may require documentation, including clinical notes and impressions, lab results, and other relevant information. The selection of references below, including the ULTOMIRIS prescribing information and published literature, may be helpful when completing the request to your patient's insurance company.

Some of the literature listed below may include content that is not included in the U.S. Food and Drug Administration (FDA)-approved US Full Prescribing Information for ULTOMIRIS. Please refer to the Indication and Important Safety Information for ULTOMIRIS on pages 3-5, including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections, and the accompanying US Full Prescribing Information.

This compendium is not inclusive of all US and global data and literature for ULTOMIRIS for anti-AQP4 antibody-positive NMOSD. Alexion does not warrant, promise, guarantee, or make any statement that the use or citation of any literature listed below will result in coverage or payment for ULTOMIRIS.

Abstracts for the references cited below are available online. Most of the publications permit access and download of the articles for personal use; some publications require that the article be purchased in order to gain access.

For ease of use, each reference is categorized by topic, as follows:

Advisory Committee on Immunization Practices (ACIP) Meningococcal Vaccination Recommendations

Murthy N, Wodi AP, McNally VV, Daley MF, Cineas S; Advisory Committee on Immunization Practices. Recommended Adult Immunization Schedule, United States, 2024. *Ann Intern Med*. 2024;177(2):221-237.

Mbaeyi SA, Bozio CH, Duffy J, et al. Meningococcal vaccination: Recommendations of the Advisory Committee on Immunization Practices, United States, 2020. *MMWR Recomm Rep*. 2020;69(9):1-41.

Collins JP, Crowe SJ, Ortega-Sanchez IR, et al. Use of the Pfizer Pentavalent Meningococcal Vaccine among persons aged ≥10 years: recommendations of the Advisory Committee on Immunization Practices – United States, 2023. *MMWR Morb Mortal Wkly Rep*. 2024;73(15):345-350.

Diagnosis

Jarius S, Aktas O, Ayzenberg I, et al. Update on the diagnosis and treatment of neuromyelits optica spectrum disorders (NMOSD) – revised recommendations of the Neuromyelitis Optica Study Group (NEMOS). Part I: Diagnosis and differential diagnosis. *J Neurol.* 2023;270(7):3341-3368.

Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. 2015;85(2):177-189.

Disability Measurement Scales

Expanded Disability Status Scale

MS Trust. Expanded Disability Status Scale (EDSS). MStrust.org. Updated September 2020. Accessed September 25, 2024. https://mstrust.org.uk/a-z/expanded-disability-status-scale-edss

Healthcare Resource Utilization

Ajmera MR, Boscoe A, Mauskopf J, Candrilli SD, Levy M. Evaluation of comorbidities and health care resource use among patients with highly active neuromyelitis optica. *J Neurol Sci*. 2018;384:96-103.

Wingerchuk DM, Zhang I, Kielhorn A, et al. Network meta-analysis of Food and Drug Administration-approved treatment options for adults with aquaporin-4 immunoglobulin G-positive neuromyelitis optica spectrum disorder. *Neurol Ther*. 2022;11(1):123-135.

Please see Important Safety Information on pages 3-5 and the full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections.

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Burden of Disease

Wingerchuk DM, Lennon VA, Lucchinetti CF, et al. The spectrum of neuromyelitis optica. *Lancet Neurol*. 2007;6(9):805-815.

Wingerchuk DM, Weinshenker BG. Neuromyelitis optica (Devic's syndrome). *Handb Clin Neurol*. 2014;122:581-599.

Wingerchuk DM, Hogancamp WF, O'Brien PC, Weinshenker BG. The clinical course of neuromyelitis optica (Devic's syndrome). *Neurology*. 1999;53(5):1107-1114.

Mutch K, Methley A, Moore P, Jacob A. Life on hold: the experience of living with neuromyelitis optica. *Disabil Rehabil*. 2014;36(13):1100-1107.

Pittock SJ, Lucchinetti CF. Neuromyelitis optica and the evolving spectrum of autoimmune aquaporin-4 channelopathies: a decade later. *Ann N Y Acad Sci*. 2016;1366(1):20-39.

Mealy MA, Boscoe A, Caro J, Levy M. Assessment of patients with neuromyelitis optica spectrum disorder using the EQ-5D. *Int J MS Care*. 2019;21(3):129-134.

Jiao Y, Fryer JP, Lennon VA, et al. Updated estimate of AQP4-IgG serostatus and disability outcome in neuromyelitis optica. *Neurology*. 2013;81(14):1197-1204.

Jarius S, Ruprecht K, Wildemann B, et al. Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: a multicentre study of 175 patients. *J Neuroinflammation*. 2012;9:14.

Kitley J, Leite MI, Nakashima I, et al. Prognostic factors and disease course in aquaporin-4 antibody-positive patients with neuromyelitis optica spectrum disorder from the United Kingdom and Japan. *Brain*. 2012;135(pt 6):1834-1849.

High-Risk Populations

Hor JY, Asgari N, Nakashima I, et al. Epidemiology of Neuromyelitis Optica Spectrum Disorder and Its Prevalence and Incidence Worldwide. *Front Neurol*. 2020;11:501.

Kim SH, Mealy MA, Levy M, et al. Racial differences in neuromyelitis optica spectrum disorder. *Neurology*. 2018;91(22):e2089-e2099.

Mealy MA, Kessler RA, Rimler Z, et al. Mortality in neuromyelitis optica is strongly associated with African ancestry. *Neurol Neuroimmunol Neuroinflamm*. 2018;5(4):e468.

Pathophysiology

Piatek P, Domowicz M, Lewkowicz N, et al. C5a-preactivated neutrophils are critical for autoimmune-induced astrocyte dysregulation in neuromyelitis optica spectrum disorder. *Front Immunol*. 2018;9:1694.

Chamberlain JL, Huda S, Whittam DH, Matiello M, Morgan BP, Jacob A. Role of complement and potential of complement inhibitors in myasthenia gravis and neuromyelitis optica spectrum disorders: a brief review. *J Neurol*. 2021;268(5):1643-1664.

Jarius S, Wildemann B. The history of neuromyelitis optica. *J Neuroinflammation*. 2013;10:8.

Winkler A, Wrzos C, Haberl M, et al. Blood-brain barrier resealing in neuromyelitis optica occurs independently of astrocyte regeneration. *J Clin Invest*. 2021;131(5):e141694.

Denial Due to Medication History

Inebilizumab. Prescribing Information. Horizon Therapeutics USA, Inc.

Cree BAC, Bennett JL, Kim HJ, et al. N-MOmentum study investigators. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial. *Lancet*. 2019 12;394(10206):1352-1363.

Rituximab. Prescribing Information. Genentech Inc.

Yamamura T, Kleiter I, Fujihara K, et al. Trial of satralizumab in neuromyelitis optica spectrum disorder. *New England Journal of Medicine*. 2019;381(22):2114-2124.

Traboulsee A, Greenberg BM, Bennett JL, et al. Safety and efficacy of satralizumab monotherapy in neuromyelitis optica spectrum disorder: a randomised, double-blind, multicentre, placebo-controlled phase 3 trial. *Lancet Neurol*. 2020;19(5):402-412.

Hinson SR, Lennon VA, Pittock SJ. Autoimmune AQP4 channelopathies and neuromyelitis optica spectrum disorders. *Handb Clin Neurol*. 2016;133:377-403.

Denial Due to Medication History (CONTINUED)
Kulkarni S, Durham H, Glover L, et al. Metabolic adverse events associated with systemic corticosteroid therapy-a systematic review and meta-analysis. *BMJ Open*. 2022;12(12):e061476.

SOLU-MEDROL. Prescribing Information. Pfizer Inc.

Balasubramanian A, Wade SW, Adler RA, Saag K, Pannacciulli N, Curtis JR. Glucocorticoid exposure and fracture risk in a cohort of US patients with selected conditions. *J Bone Miner Res*. 2018;33(10):1881-1888.

Satralizumab. Prescribing Information. Genentech, Inc.

ULTOMIRIS Prescribing Information and Publications in NMOSD
ULTOMIRIS. Prescribing Information. Alexion Pharmaceuticals, Inc.

Clardy, S.L., Pittock, S.J., Aktas, O. et al. Network meta-analysis of ravulizumab and alternative interventions for the treatment of neuromyelitis optica spectrum disorder. *Neurol Ther.* 2024;13:535-54.

Pittock SJ, Barnett M, Bennett JL, et al. Ravulizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. *Ann Neurol*. 2023;93(6):1053-1068.

Ortiz S, Pittock S, Berthele A, et al. Pharmacokinetics and pharmacodynamics of ravulizumab in adults with anti-aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder during the phase 3 CHAMPION-NMOSD trial. *Neurology*. 2023;100(17)(supp 2):3713.

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

INDICATION

ULTOMIRIS is indicated for the treatment of adult patients with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody positive.

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 4 and 5 and the full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections.

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IMPORTANT SAFETY INFORMATION (CONTINUED)

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.

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.

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IMPORTANT SAFETY INFORMATION (CONTINUED)

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.

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