A Compendium of Paroxysmal Nocturnal Hemoglobinuria (PNH) References for ULTOMIRIS® (ravulizumab-cwvz)

INDICATION & SELECT IMPORTANT SAFETY INFORMATION

INDICATION

ULTOMIRIS is indicated for the treatment of adult and pediatric patients one month of age and older with paroxysmal nocturnal hemoglobinuria (PNH).

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)*].

When completing a prior authorization (PA), precertification, reauthorization, or appeal request for ULTOMIRIS in the treatment of adults and pediatric patients one month of age and older with PNH, 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 FDA-approved US full Prescribing Information for ULTOMIRIS. Please refer to the Indication and Important Safety Information for ULTOMIRIS on pages 1, 4, and 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 PNH. 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.

Note: the tool does not provide the actual articles or references within.

All content within is factual information and does not make any statement that leveraging these citations or literature will result in coverage or payment for ULTOMIRIS. For ease of use, each reference is categorized by primary topic, as follows:

ULTOMIRIS PRESCRIBING INFORMATION AND PUBLICATIONS IN PNH:

- ULTOMIRIS. Prescribing information. Alexion Pharmaceuticals, Inc.
- US Food and Drug Administration, Department of Health and Human Services. ULTOMIRIS sBLA 761108 approval letter, December 21, 2018. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/761108Orig1s000Ltr.pdf

Clinical Efficacy and Safety

- Lee JW, Sicre de Fontbrune F, Wong Lee Lee L, et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. *Blood*. 2019;133(6):530-539.
- Kulasekararaj AG, Hill A, Rottinghaus ST, et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. *Blood*. 2019;133(6):540-549.
- Schrezenmeier H, Kulasekararaj A, Mitchell L, et al. One-year efficacy and safety of ravulizumab in adults with paroxysmal nocturnal hemoglobinuria naïve to complement inhibitor therapy: open-label extension of a randomized study. *Ther Adv Hematol*. 2020;11:2040620720966137.
- Kulasekararaj AG, Hill A, Langemeijer S, et al. One-year outcomes from a phase 3 randomized trial of ravulizumab in adults with paroxysmal nocturnal hemoglobinuria who received prior eculizumab. *Eur J Haematol*. 2021;106(3):389-397.
- Kulasekararaj AG, Griffin M, Langemeijer S, et al. Long-term safety and efficacy of ravulizumab in patients with paroxysmal nocturnal hemoglobinuria: 2-year results from two pivotal phase 3 studies. *Eur J Haematol*. 2022;109(3):205-214.

Bone Marrow Disorder

- Risitano A, Jang JH, Gyeong-Won L, et al. Transfusion requirements in adult patients with paroxysmal nocturnal hemoglobinuria with or without a history of bone marrow disorder receiving ravulizumab and eculizumab: results from a phase 3 non-inferiority study extension. *Blood*. 2020;136(suppl 1):31-33.

Geriatric Patients

- De Latour RP, Szer J, Kulasekararaj A, et al. Efficacy and safety of ravulizumab in older patients aged >65 years with paroxysmal nocturnal hemoglobinuria in the 301 and 302 phase 3 extension studies. *Blood*. 2020;136(suppl 1):42-43.

Breakthrough Hemolysis

- Brodsky RA, Peffault de Latour R, Rottinghaus ST, et al. Characterization of breakthrough hemolysis events observed in the phase III randomized studies of ravulizumab versus eculizumab in adults with paroxysmal nocturnal hemoglobinuria. *Haematologica*. 2021;106(1):230-237.

Thrombosis

- Hill A, Kelly RJ, Hillmen P. Thrombosis in paroxysmal nocturnal hemoglobinuria. *Blood*. 2013;121(25):4985-5105.
- Peffault de Latour R, Hill A, Füreder W, et al. Ravulizumab reduces the risk of thrombosis in adult patients with paroxysmal nocturnal hemoglobinuria and high disease activity: 2-year data from a phase III, open-label study. *HemaSphere*. 2021;5(S2):109-110.

Immunosuppressant Use

- Schrezenmeier H, Wook Lee J, Hill A, et al. Efficacy and safety of concomitant use of ravulizumab and IST in patients with paroxysmal nocturnal hemoglobinuria up to 52 weeks. *Blood*. 2020;136(suppl 1):37-38.

Pharmacokinetic and Pharmacodynamic Complement Component 5 Inhibition

- Peffault de Latour R, Brodsky RA, Ortiz S, et al. Pharmacokinetic and pharmacodynamic effects of ravulizumab and eculizumab on complement component 5 in adults with paroxysmal nocturnal haemoglobinuria: results of two phase 3 randomised, multicentre studies. *Br J Haematol*. 2020;191(3):476-485.

Transfusions

- Nagalla S, Hill A, Royston M, Tomazos I. Ravulizumab and eculizumab reduce transfusions in adult patients with paroxysmal nocturnal hemoglobinuria: evidence from three real-world databases: Trinetx US EMR, Trinetx US Claims and Komodo Health. *HemaSphere*. 2021;5(S2):645-646.

Please see Important Safety Information on pages 1 and 4-5 and accompanying full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections.

Lactate Dehydrogenase

- Lee JW, Jang JH, Kim JS, et al. Clinical signs and symptoms associated with increased risk for thrombosis in patients with paroxysmal nocturnal hemoglobinuria from a Korean Registry. *Int J Hematol*. 2013;97(6):749-757.
- Jang JH, Kim JS, Yoon SS, et al. Predictive factors of mortality in population of patients with paroxysmal nocturnal hemoglobinuria (PNH): results from a Korean PNH registry. *J Korean Med Sci*. 2016;31(2):214-221.
- Jang JH, Kim JS, Lim CTK, et al. Impact of lactate dehydrogenase and hemoglobin levels on clinical outcomes in patients with paroxysmal nocturnal hemoglobinuria: results from the national Korean PNH registry. *J Korean Med Sci*. 2024;39(8):e81.

Fatigue

- Schrezenmeier H, Kulasekararaj AG, Mitchell L, et al. Predictors for improvement in patient-reported outcomes: *post-hoc* analysis of a phase 3 randomized, open-label study of eculizumab and ravulizumab in complement inhibitor-naïve patients with paroxysmal nocturnal hemoglobinuria (PNH). *Blood*. 2021;138(suppl 1):2196.

BURDEN OF DISEASE:

- Nishimura JI, Kanakura Y, Ware RE, et al. Clinical course and flow cytometric analysis of paroxysmal nocturnal hemoglobinuria in the United States and Japan. *Medicine (Baltimore)*. 2004;83(3):193-207.
- Jang JH, Kim JS, Yoon SS, et al. Predictive factors of mortality in population of patients with paroxysmal nocturnal hemoglobinuria (PNH): results from a Korean PNH registry. *J Korean Med Sci*. 2016;31(2):214-221.
- Jalbert JJ, Chaudhari U, Zhang H, Weyne J, Shammo JM. Epidemiology of PNH and real-world treatment patterns following an incident PNH diagnosis in the US. *Blood*. 2019;134(suppl 1):3407.
- Schrezenmeier H, Röth A, Araten DJ, et al. Baseline clinical characteristics and disease burden in patients with paroxysmal nocturnal hemoglobinuria (PNH): updated analysis from the International PNH Registry. *Ann Hematol*. 2020;99(7):1505-1514.
- Lee JW, Jang JH, Kim JS, et al. Clinical signs and symptoms associated with increased risk for thrombosis in patients with paroxysmal nocturnal hemoglobinuria from a Korean Registry. *Int J Hematol*. 2013;97(6):749-757.

PATHOPHYSIOLOGY:

- Brodsky RA. *Hematology – Basic Principles and Practice*. 7th ed. Elsevier; 2018:415-424.
- Hill A, DeZern AE, Kinoshita T, Brodsky RA. Paroxysmal nocturnal haemoglobinuria. *Nat Rev Dis Primers*. 2017;3:17028.
- Hill A, Kelly RJ, Hillmen P. Thrombosis in paroxysmal nocturnal hemoglobinuria. *Blood*. 2013;121(25):4985-4996.

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP) MENINGOCOCCAL VACCINATION RECOMMENDATIONS:

- Freedman M, Kroger A, Hunter P, Ault KA; Advisory Committee on Immunization Practices. Recommended Adult Immunization Schedule, United States, 2020. *Ann Intern Med*. 2020;172(5):337-347.
- 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. doi:10.15585/mmwr.rr6909a1

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

Please see Important Safety Information on pages 1 and 4-5 and accompanying full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections.

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

WARNINGS AND PRECAUTIONS (cont'd)

Monitoring Disease Manifestations after ULTOMIRIS Discontinuation

After discontinuing treatment with ULTOMIRIS, closely monitor for signs and symptoms of hemolysis, identified by elevated LDH along with sudden decrease in PNH clone size or hemoglobin, or re-appearance of symptoms such as fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction. Monitor any patient who discontinues ULTOMIRIS for at least 16 weeks to detect hemolysis and other reactions. If signs and symptoms of hemolysis occur after discontinuation, including elevated LDH, consider restarting treatment with ULTOMIRIS.

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

Adverse reactions reported in ≥10% or more of patients with PNH were upper respiratory tract infection and headache. Serious adverse reactions were reported in 15 (6.8%) patients receiving ULTOMIRIS. The serious adverse reactions in patients treated with ULTOMIRIS included hyperthermia and pyrexia. No serious adverse reaction was reported in more than 1 patient treated with ULTOMIRIS. One fatal case of sepsis was identified in a patient treated with ULTOMIRIS. In clinical studies, clinically relevant adverse reactions in 1% of adult patients include infusion-related reactions.

Adverse reactions reported in ≥10% of pediatric patients treated with ULTOMIRIS who were treatment-naïve vs. Eculizumab-experienced were anemia (20% vs. 25%), abdominal pain (0% vs. 38%), constipation (0% vs. 25%), pyrexia (20% vs. 13%), upper respiratory tract infection (20% vs. 75%), pain in extremity (0% vs. 25%), and headache (20% vs. 25%).

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