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

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

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.**

ULTOMIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the ULTOMIRIS REMS, prescribers must enroll in the program. Enrollment in the ULTOMIRIS REMS program and additional information are available by telephone: 1-888-765-4747 or at www.ultomirisrems.com.

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 meningococcal infections/sepsis**, 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 of ULTOMIRIS or SOLIRIS. 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.

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

- 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.

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

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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.

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.

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.

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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

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

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.

WARNINGS AND PRECAUTIONS

Serious Meningococcal Infections

Risk and Prevention

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. If ULTOMIRIS must be initiated immediately in an unvaccinated patient, administer meningococcal vaccine(s) as soon as possible and provide 2 weeks of antibacterial drug prophylaxis.

In clinical studies, 59 adult patients with PNH were treated with ULTOMIRIS less than 2 weeks after meningococcal vaccination. All of these patients received antibiotics for prophylaxis of meningococcal infection until at least 2 weeks after meningococcal vaccination. The benefits and risks of antibiotic prophylaxis for prevention of meningococcal infections in patients receiving ULTOMIRIS have not been established. In PNH clinical studies in adult patients, 3 out of 261 PNH patients developed serious meningococcal infections/sepsis while receiving treatment with ULTOMIRIS; all 3 had been vaccinated. These 3 patients recovered while continuing treatment with ULTOMIRIS. Consider discontinuation of ULTOMIRIS in patients who are undergoing treatment for serious meningococcal infection.

REMS

Under the ULTOMIRIS REMS, prescribers must enroll in the program due to the risk of meningococcal infections. 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.

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

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

WARNINGS AND PRECAUTIONS (cont.)

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
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 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 and limb discomfort, drug hypersensitivity (allergic reaction), dysgeusia (bad taste), and drowsiness. These reactions did not require discontinuation of ULTOMIRIS. Interrupt infusion and institute supportive measures if signs of cardiovascular instability or respiratory compromise occur.

ADVERSE REACTIONS

Adverse reactions reported in 5% or more of patients treated with ULTOMIRIS vs. Eculizumab was Upper respiratory tract infection (39% vs. 39%), Headache (32% vs. 26%), Diarrhea (9% vs. 5%), Nausea (9% vs. 9%), Pyrexia (7% vs. 8%), Pain in extremity (6% vs. 5%), Abdominal pain (6% vs. 7%), Dizziness (5% vs. 6%), Arthralgia (5% vs. 5%). 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% or more of pediatric patients treated with ULTOMIRIS who were treatment-naïve vs. Eculizumab-experienced was 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%), 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.

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ALEXION®
AstraZeneca Rare Disease