ULTOMIRIS®
(ravulizumab-cwvz)
injection for intravenous use
300 mg/3 mL vial

ULTOMIRIS is for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH)

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.

INDICATION

ULTOMIRIS is indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

SELECT IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

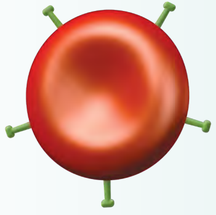
- Patients with unresolved *Neisseria meningitidis* infection.
- Patients who are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying ULTOMIRIS treatment outweigh the risks of developing a meningococcal infection.

Please see Important Safety Information throughout and on page 15. Please see accompanying full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.

PNH is a chronic, catastrophic disease characterized by complement-mediated intravascular hemolysis[2-4]

PNH IS A HEMOLYTIC DISEASE THAT ORIGINATES IN THE HEMATOPOIETIC STEM CELL[3-5]

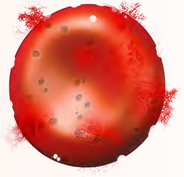
Normal blood cell



GPI-anchored proteins

In healthy RBCs, GPI-anchored proteins (CD55 and CD59)[a] defend against complement-mediated hemolysis.

PNH blood cell



No GPI-anchored proteins

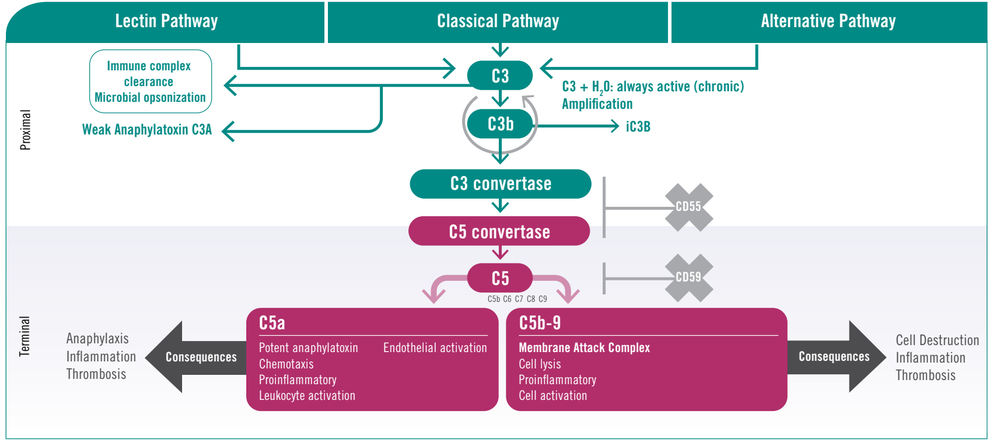
In PNH, an acquired *PIG-A* mutation can lead to the complete or partial absence of GPI-anchored proteins.

[a]Complement-regulatory proteins CD55 (decay-accelerating factor) and CD59 (membrane inhibitor of reactive lysis) defend against the complement pathway by regulating the formation and stability of the C3 convertase and blocking the assembly of the membrane attack complex, respectively.[6]

GPI=glycosylphosphatidylinositol; *PIG-A*=phosphatidylinositol glycan anchor biosynthesis class A; RBC=red blood cell.

The continuously active system attacks defective RBCs, causing intravascular hemolysis, the underlying cause of progressive morbidities, which results in potentially life-threatening complications of intravascular hemolysis.[7-13]

Complement attack leads to devastating systemic consequences in PNH[12-14]



Graphic is a simplified representation of the complement cascade.
MAC=membrane attack complex.

- Terminal complement activation begins with cleavage of C5, resulting in the formation of the MAC, and intravascular hemolysis[15]

Control of C5 levels plays an important role in effectively managing PNH[2,3,16]

ULTOMIRIS is for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH)

THE FIRST AND ONLY LONG-ACTING COMPLEMENT INHIBITOR THAT PROVIDES IMMEDIATE AND COMPLETE C5 INHIBITION SUSTAINED FOR 8 WEEKS[1,17-19,a]

- ULTOMIRIS, built on the foundation of eculizumab, has a ~4x longer half-life[b]
- ULTOMIRIS was studied in the largest phase 3 PNH program encompassing a clinically diverse patient population, including complement inhibitor–naïve and eculizumab-treated patients
- ULTOMIRIS demonstrated robust and sustained efficacy across all endpoints vs eculizumab in noninferiority studies, while allowing patients every-8-week dosing
- The ULTOMIRIS safety profile was similar to that of eculizumab as observed in the largest phase 3 PNH clinical program
- ULTOMIRIS resulted in a reduction of free C5 levels in the blood, which was correlated with maximal intravascular hemolysis control in clinical studies
- ULTOMIRIS has weight-based dosing with 6-7 infusions per year[a]
- The serious adverse reactions in patients treated with ULTOMIRIS included hyperthermia and pyrexia

[a]Starting 2 weeks after the initial loading dose, maintenance doses are administered once every 8 weeks.
[b]The mean (%CV) terminal elimination half-life and clearance of ravulizumab-cwvz in patients with PNH are 49.7 (18.0) days and 0.08 (29.5) L/day, respectively. Half-life of eculizumab is 11.25 to 17.25 days.
CV=coefficient of variation.

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

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- 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.

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SELECT IMPORTANT SAFETY INFORMATION

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.

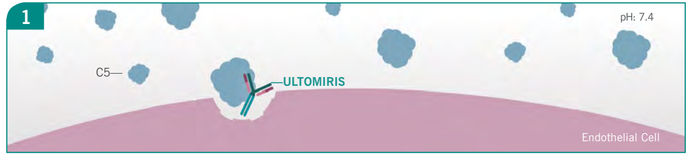
One fatal case of sepsis was identified in a patient treated with ULTOMIRIS.

Please see Important Safety Information throughout and on page 15. Please see accompanying full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.

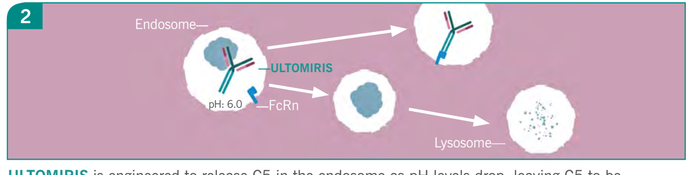
To learn more, visit www.ULTOMIRIS.com

ULTOMIRIS, built on the foundation of eculizumab, has a ~4x longer half-life[1,17,20,a,b]

Pharmacology based on preclinical studies of ULTOMIRIS[a]

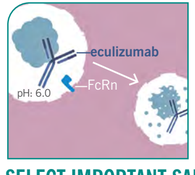


Both **ULTOMIRIS** and eculizumab bind to C5 in the bloodstream and prevent its activation.



ULTOMIRIS is engineered to release C5 in the endosome as pH levels drop, leaving C5 to be degraded by the lysosome while allowing **ULTOMIRIS** to use a natural pathway to recycle back into the bloodstream via FcRn.

ULTOMIRIS has also been engineered to bind to FcRn with greater affinity. Through these modifications, **ULTOMIRIS** has a ~4x longer half-life than eculizumab, and provides immediate, complete, and sustained inhibition of C5 for 8 weeks.



ULTOMIRIS differs from eculizumab in how it behaves after binding to C5. For eculizumab, binding to C5 inhibits FcRn-mediated recycling, leading to its lysosomal degradation along with C5.

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Serious Meningococcal Infection

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.

Please see Important Safety Information throughout and on page 15.
Please see accompanying full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.

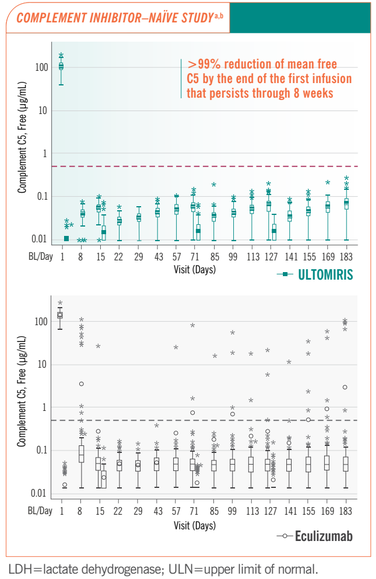
[a]Targeted engineering to incorporate 4 amino acid substitutions designed to reduce target-mediated drug disposition and enhance FcRn-mediated recycling into eculizumab has led to the generation of ULTOMIRIS, which exhibited an extended duration of action in preclinical models relative to eculizumab.

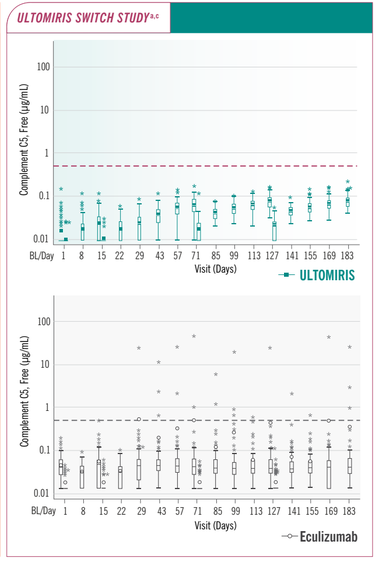
[b]The mean (%CV) terminal elimination half-life and clearance of ravulizumab-cwvz in patients with PNH are 49.7 (18.0) days and 0.08 (29.5) L/day, respectively. Half-life of eculizumab is 11.25 to 17.25 days.

FcRn=human neonatal Fc receptor.

ULTOMIRIS provided immediate, complete, and sustained C5 inhibition in clinical studies[1,18,19,21]

Mean free C5 levels over time in patients treated with ULTOMIRIS and eculizumab





LDH=lactate dehydrogenase; ULN=upper limit of normal.

Patients treated with ULTOMIRIS experienced fewer instances of breakthrough hemolysis vs those treated with eculizumab

- Breakthrough hemolysis was defined as at least 1 new or worsening symptom or sign of intravascular hemolysis in the presence of elevated LDH ≥2x ULN, after prior LDH reduction to <1.5x ULN on therapy
- In the complement inhibitor–naïve study, 4.0% of patients treated with ULTOMIRIS experienced breakthrough hemolysis vs 10.7% with eculizumab
- In the ULTOMIRIS switch study, no patients treated with ULTOMIRIS experienced breakthrough hemolysis vs 5.1% of patients treated with eculizumab

[a]The horizontal line in the middle of each box indicates the median, a square indicates the mean for ULTOMIRIS, and a circle indicates the mean for eculizumab. The top and bottom borders of the box mark the 75th and 25th percentiles, respectively. The whiskers represent the 1.5 interquartile range (IQR) of the lower quartile and upper quartile. Outliers are represented by asterisks beyond the whiskers. Dashed horizontal lines indicate serum-free C5 concentration of 0.5 µg/mL.

[b]The complement inhibitor–naïve study [ALXN1210-PNH-301; NCT02946463] was a 26-week, multicenter, open-label, randomized, active-controlled, noninferiority, phase 3 study conducted in 246 patients naïve to complement inhibitor treatment prior to study entry.

[c]The ULTOMIRIS switch study [ALXN1210-PNH-302; NCT03056040] was a 26-week, multicenter, open-label, randomized, active-controlled, noninferiority, phase 3 study conducted in 195 patients with PNH who were clinically stable after having been treated with eculizumab for at least the past 6 months.

A Gyros-based fluorescence assay was used for patients who received ULTOMIRIS, and an electrochemiluminescence immunoassay was used for patients who received eculizumab. Baseline was defined as the last nonmissing value before the first dose of study drug.

Free C5 levels below 0.5 µg/mL were correlated with maximal intravascular hemolysis control and complete terminal complement inhibition in clinical studies

SELECT IMPORTANT SAFETY INFORMATION

Risk and Prevention (continued)

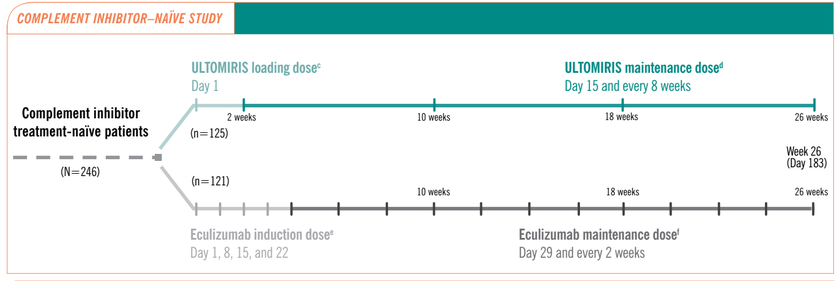
If ULTOMIRIS must be initiated immediately in an unvaccinated patient, administer meningococcal vaccine(s) as soon as possible and provide 2 weeks of antibacterial drug prophylaxis.

ULTOMIRIS® (ravulizumab-cwvz) injection for intravenous use 300 mg/3 mL vial

ULTOMIRIS was studied in the largest phase 3 PNH program encompassing a clinically diverse patient population, including complement inhibitor–naïve and eculizumab-treated patients[1,18,19]

ULTOMIRIS was evaluated in 2 phase 3, open-label, randomized, active-controlled, multicenter, noninferiority studies

- The efficacy and safety of ULTOMIRIS were assessed in adult (≥18 years of age) patients with PNH **who were naïve to eculizumab**[a,b]



Complement Inhibitor–Naïve Study Endpoints

Co-Primary	Secondary
• Transfusion avoidance[g] • LDH normalization	• Percent change from baseline in LDH levels • Change in fatigue (FACIT-Fatigue) • Proportion of patients with breakthrough hemolysis[h] • Proportion of patients with stabilized hemoglobin

- Vaccinate patients for meningococcal disease according to current Advisory Committee on Immunization Practices (ACIP) guidelines to reduce the risk of serious infection
- Provide 2 weeks of antibacterial drug prophylaxis to patients if ULTOMIRIS must be initiated immediately and vaccines are administered less than 2 weeks before starting ULTOMIRIS therapy

[a]Population included male and female patients ≥18 years of age in 25 countries.

[b]In the complement inhibitor–naïve study, 98% of patients had a documented PNH-associated condition diagnosed prior to enrollment in the trial: anemia (85%), hemoglobinuria (63%), history of aplastic anemia (32%), history of renal failure (12%), myelodysplastic syndrome (5%), pregnancy complications (3%), and other (16%).

[c]Loading dose for patients weighing ≥40 to <60 kg=2400 mg; loading dose for patients weighing ≥60 to <100 kg=2700 mg; loading dose for patients weighing ≥100 kg=3000 mg.

[d]Maintenance dose for patients weighing ≥40 to <60 kg=3000 mg; maintenance dose for patients weighing ≥60 to <100 kg=3300 mg; maintenance dose for patients weighing ≥100 kg=3600 mg.

[e]Eculizumab induction dose=600 mg.

[f]Eculizumab maintenance dose=900 mg.

[g]Transfusion avoidance was considered as achieved only by the patients who did not receive a transfusion and did not meet the protocol-specified guidelines for transfusion from baseline to Day 183.

[h]Breakthrough hemolysis was defined as at least 1 new or worsening symptom or sign of intravascular hemolysis in the presence of elevated LDH ≥2x ULN, after prior LDH reduction to <1.5x ULN on therapy.

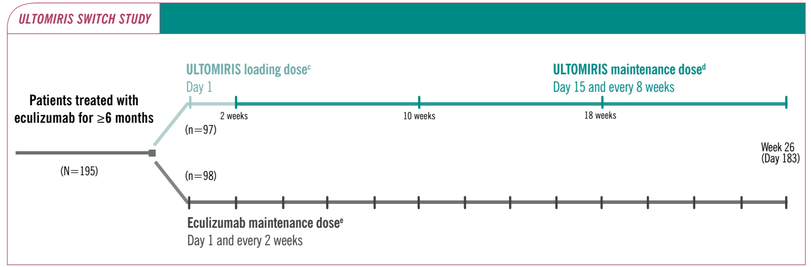
FACIT=Functional Assessment of Chronic Illness Therapy.

SELECT IMPORTANT SAFETY INFORMATION

Risk and Prevention (continued)

In clinical studies, 59 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, 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.

- The efficacy and safety of ULTOMIRIS were assessed in adult (≥18 years of age) patients with PNH **who were treated with and clinically stable on eculizumab for ≥6 months**[a,b]



ULTOMIRIS Switch Study Endpoints

Primary	Secondary
• LDH percent change from baseline	• Proportion of patients with breakthrough hemolysis[f] • Change in fatigue (FACIT-Fatigue) • Transfusion avoidance[g] • Proportion of patients with stabilized hemoglobin

Across both studies, the clinically diverse patient population included males and females aged ≥18 years in up to 25 countries, with red and white blood cell clone sizes of ≥5% with and without a history of aplastic anemia

[a]Population included male and female patients ≥18 years of age in 11 countries.

[b]In the ULTOMIRIS switch study, 95% of patients had a documented PNH-associated condition diagnosed prior to enrollment in the trial: anemia (67%), hematuria or hemoglobinuria (49%), history of aplastic anemia (37%), history of renal failure (9%), myelodysplastic syndrome (5%), pregnancy complication (7%), and other (14%).

[c]Loading dose for patients weighing ≥40 to <60 kg=2400 mg; loading dose for patients weighing ≥60 to <100 kg=2700 mg; loading dose for patients weighing ≥100 kg=3000 mg.

[d]Maintenance dose for patients weighing ≥40 to <60 kg=3000 mg; maintenance dose for patients weighing ≥60 to <100 kg=3300 mg; maintenance dose for patients weighing ≥100 kg=3600 mg.

[e]Eculizumab maintenance dose=900 mg.

[f]Breakthrough hemolysis was defined as at least 1 new or worsening symptom or sign of intravascular hemolysis in the presence of elevated LDH ≥2x ULN, after prior LDH reduction to <1.5x ULN on therapy.

[g]Transfusion avoidance was considered as achieved only by the patients who did not receive a transfusion and did not meet the protocol-specified guidelines for transfusion from baseline to Day 183.

SELECT IMPORTANT SAFETY INFORMATION

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.

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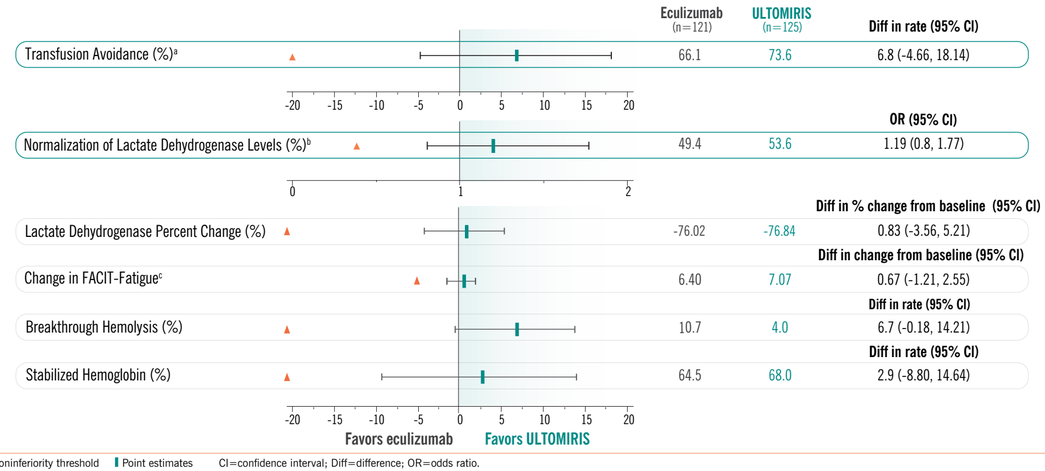
ULTOMIRIS® (ravulizumab-cwvz) injection for intravenous use 300 mg/3 mL vial

ULTOMIRIS demonstrated robust and sustained efficacy across all endpoints vs eculizumab in noninferiority studies, while allowing patients every-8-week dosing[1,18,19]

COMPLEMENT INHIBITOR–NAÏVE STUDY

EFFICACY RESULTS ACROSS PRIMARY AND SECONDARY ENDPOINTS



▲ Noninferiority threshold ▌Point estimates CI=confidence interval; Diff=difference; OR=odds ratio.

[a]For the transfusion avoidance endpoint, treatment differences (95% CIs) are based on estimated differences in percent with 95% CI.

[b]For the lactate dehydrogenase normalization endpoint, the adjusted prevalence within each treatment is displayed.

[c]There was no observable difference in fatigue between ULTOMIRIS and eculizumab after 26 weeks of treatment compared with baseline, as measured by the FACIT-Fatigue instrument. Patient-reported fatigue may be an under- or overestimation, because patients were not blinded to treatment assignment.

ULTOMIRIS demonstrated robust and sustained efficacy across a clinically diverse patient population

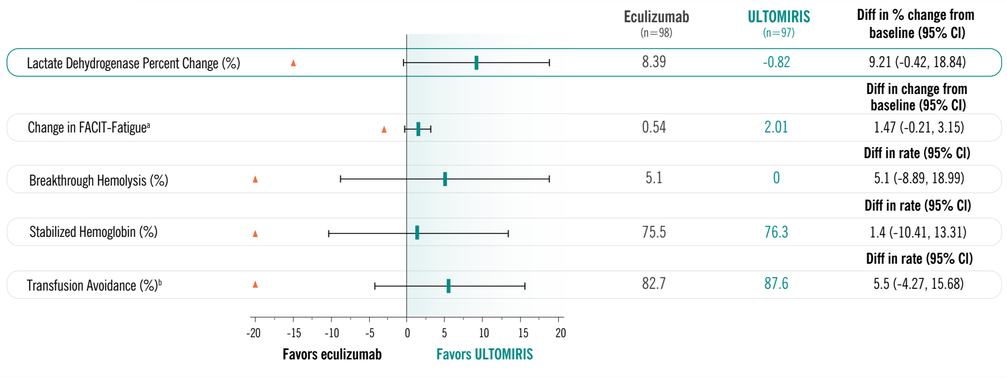
SELECT IMPORTANT SAFETY INFORMATION

Other Infections

Patients may have increased susceptibility to encapsulated bacteria infections, especially infections caused by *Neisseria meningitidis* but also *Streptococcus pneumoniae*, *Haemophilus influenzae*, and to a lesser extent, *Neisseria gonorrhoeae*. If ULTOMIRIS is administered to patients with active systemic infections, monitor closely for worsening infection.

ULTOMIRIS SWITCH STUDY

EFFICACY RESULTS ACROSS PRIMARY AND SECONDARY ENDPOINTS



▲ Noninferiority threshold ▌Point estimates

[a]There was no observable difference in fatigue between ULTOMIRIS and eculizumab after 26 weeks of treatment compared with baseline, as measured by the FACIT-Fatigue instrument. Patient-reported fatigue may be an under- or overestimation, because patients were not blinded to treatment assignment.

[b]For the transfusion avoidance endpoint, treatment differences (95% CIs) are based on estimated differences in percent with 95% CI.

Patients treated with eculizumab were effectively switched to ULTOMIRIS

SELECT IMPORTANT SAFETY INFORMATION

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 reappearance 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.

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The ULTOMIRIS safety profile was similar to that of eculizumab as observed in the largest phase 3 PNH clinical program[1]

ADVERSE EVENTS REPORTED IN 5% OR MORE OF ULTOMIRIS-TREATED PATIENTS IN COMPLEMENT INHIBITOR–NAÏVE AND ECULIZUMAB-EXPERIENCED STUDIES

	Number (%) of Patients	
System Organ Class Preferred Term	Eculizumab n=219	ULTOMIRIS n=222
Gastrointestinal disorders		
Diarrhea	**12** (5)	**19** (9)
Nausea	**19** (9)	**19** (9)
Abdominal pain	**16** (7)	**13** (6)
General disorders and administration site conditions		
Pyrexia	**18** (8)	**15** (7)
Infections and infestations		
Upper respiratory tract infection[a]	**86** (39)	**86** (39)
Musculoskeletal and connective tissue disorders		
Pain in extremity	**11** (5)	**14** (6)
Arthralgia	**12** (5)	**11** (5)
Nervous system disorders		
Headache	**57** (26)	**71** (32)
Dizziness	**14** (6)	**12** (5)

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- The most frequent adverse reactions (≥10%) with ULTOMIRIS 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

[a]Includes the preferred terms nasopharyngitis, upper respiratory tract infection, oropharyngeal pain, viral upper respiratory tract infection, rhinitis, respiratory tract infection, rhinorrhea, pharyngitis, and upper respiratory tract inflammation.

ULTOMIRIS has weight-based dosing with 6-7 infusions per year[1,a]

The recommended dosing regimen for adults with PNH consists of a loading dose followed by maintenance doses

PATIENTS STARTING ULTOMIRIS WITH NO PRIOR TREATMENT

Starting 2 weeks after the initial loading dose, maintenance doses are administered **once every 8 weeks.**

PATIENTS SWITCHING FROM ECULIZUMAB TO ULTOMIRIS

Loading dose of ULTOMIRIS should be administered **2 weeks after the last eculizumab infusion.**

Maintenance doses are administered **once every 8 weeks, starting 2 weeks after the loading dose.**

Dosing ULTOMIRIS

WEIGHT-BASED DOSING REGIMEN[b]

Body Weight Range (kg)[c]	Loading Dose (mg)	Maintenance Dose (mg) and Dosing Interval	
40 to <60	2,400	3,000	Every 8 weeks
60 to <100	2,700	3,300	
100 or greater	3,000	3,600	

[a]Starting 2 weeks after the initial loading dose, maintenance doses are administered once every 8 weeks.

[b]The dosing schedule is allowed to occasionally vary within 7 days of the scheduled infusion day (except for the first maintenance dose of (ULTOMIRIS); but the subsequent doses should be administered according to the original schedule.

[c]Body weight at time of treatment.

- Vaccinate patients for meningococcal disease according to current ACIP guidelines to reduce the risk of serious infection
- Provide 2 weeks of antibacterial drug prophylaxis to patients if ULTOMIRIS must be initiated immediately and vaccines are administered less than 2 weeks before starting ULTOMIRIS therapy

Continuation of ULTOMIRIS in appropriate patients with PNH is important to sustain clinical benefits

Patients who discontinue ULTOMIRIS should be monitored 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.

SELECT IMPORTANT SAFETY INFORMATION

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. In clinical trials, 5 out of 296 patients treated with ULTOMIRIS experienced infusion-related reactions (lower back pain, drop in blood pressure, infusion-related pain, elevation in blood pressure and limbs discomfort) during ULTOMIRIS administration which did not require discontinuation. Interrupt infusion and institute supportive measures if signs of cardiovascular instability or respiratory compromise occur.

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ULTOMIRIS® (ravulizumab-cwvz) injection for intravenous use 300 mg/3 mL vial

OneSource™ is here to help

ONESOURCE™
Personalized Patient Support from Alexion

Contact OneSource at 1-888-765-4747

Alexion Case Managers, with advanced PNH disease education experience and health insurance information, will be assigned to each patient to provide complimentary education and support.

The Alexion OneSource Copay Program is an Alexion-sponsored program that provides financial assistance by covering eligible commercially-insured patients' out-of-pocket costs relating to medication and infusion. Additional terms and conditions apply. Please contact OneSource with additional questions.

Alexion Case Managers assist with:

Education

- Providing your patients with educational resources and materials related to PNH
- Helping to answer your patients' questions about the disease or treatment logistics

Health insurance information

- Helping your patients understand ULTOMIRIS health insurance coverage
- Exploring alternative funding options and financial resources

Continuity of care

- Personalized support for your patients in maintaining therapy during their major life events, such as a change in job, insurance status, provider, or relocation

Community connections

- Providing information to patients regarding in-person and online meetings and events
- Connecting patients with other people living with PNH

For more information on support resources for PNH, please visit: •AlexionOneSource.com •ULTOMIRIS.com •ULTOMIRISREMS.com •AAMDS.org

References: 1. ULTOMIRIS® [prescribing information]. Boston, MA: Alexion Pharmaceuticals, Inc; October 2020. **2.** Hill A, Rother RP, Wang X, et al. *Br J Haematol*. 2010;149(3):414-425. **3.** Parker CJ. *Hematology Am Soc Hematol Educ Program*. 2016;2016(1):208-216. **4.** Borowitz MJ, Craig FE, DiGiuseppe JA, et al. *Cytometry B Clin Cytom*. 2010;78(4):211-230. **5.** Parker CJ. *Hematology Am Soc Hematol Educ Program*. 2011;2011:21-29. **6.** Brodsky RA. *Hematology: Basic Principles and Practice*. 4th ed. Philadelphia, PA: Elsevier Churchill Livingstone; 2005:419-427. **7.** Weitz I et al. *Intern Med J*. 2013;43(3):298-307. **8.** Jang JH, Kim JS, Yoon SS, et al. *J Korean Med Sci*. 2016;31(2):214-221. **9.** de Latour RP, Mary JY, Salanoubat C, et al. *Blood*. 2008;112(8):3099-3106. **10.** Loschi M, Porcher R, Barraco F, et al. *Am J Hematol*. 2016;91(4):366-370. **11.** Nishimura J-I et al. *Medicine (Baltimore)*. 2004;83(3):193-207. **12.** Murphy K. *Janeway's Immunobiology*. 8th ed. New York, NY: Garland Science, Taylor & Francis Group LLC; 2012:37-71. **13.** Kelly R, Richards S, Hillmen P, Hill A. *Ther Clin Risk Manag*. 2009;5:911-921. **14.** Walport MJ. *N Engl J Med*. 2001;344(14):1058-1066. **15.** Brodsky RA. *Blood*. 2014;124(18):2804-2811. **16.** Hillmen P, Muus P, Röth A, et al. *Br J Haematol*. 2013;162(1):62-73. **17.** Soliris [prescribing information]. Boston, MA: Alexion Pharmaceuticals, Inc; June 2019. **18.** Lee JW, Sicre de Fontbrune F, Wong Lee Lee L, et al. *Blood*. 2019;133(6):530-539. **19.** Kulasekararaj AG, Hill A, Rottinghaus ST, et al. *Blood*. 2019;133(6):540-549. **20.** Sheridan D, Yu ZX, Zhang Y, et al. *PLoS One*. 2018;13(4):e0195909. **21.** Data on file. Alexion Pharmaceuticals, Inc. 2019.

INDICATION

ULTOMIRIS is indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

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.

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 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, 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.

Other Infections

Patients may have increased susceptibility to encapsulated bacteria infections, especially infections caused by *Neisseria meningitidis* but also *Streptococcus pneumoniae*, *Haemophilus influenzae*, and to a lesser extent, *Neisseria gonorrhoeae*. 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 reappearance of symptoms such as fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), major a dverse 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. In clinical trials, 5 out of 296 patients treated with ULTOMIRIS experienced infusion-related reactions (lower back pain, drop in blood pressure, infusion-related pain, elevation in blood pressure and limbs discomfort) during ULTOMIRIS administration which did not require discontinuation. 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.

Please see accompanying full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.

ULTOMIRIS®
(ravulizumab-cwvz)
injection for intravenous use
300 mg/3 mL vial

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injection for intravenous use
300 mg/3 mL vial

ULTOMIRIS is for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH)

THE FIRST AND ONLY LONG-ACTING COMPLEMENT INHIBITOR THAT PROVIDES IMMEDIATE AND COMPLETE C5 INHIBITION SUSTAINED FOR 8 WEEKS[1,17-19,a]

- ULTOMIRIS, built on the foundation of eculizumab, has a ~4x longer half-life[b]
- ULTOMIRIS was studied in the largest phase 3 PNH program encompassing a clinically diverse patient population, including complement inhibitor–naïve and eculizumab-treated patients
- ULTOMIRIS demonstrated robust and sustained efficacy across all endpoints vs eculizumab in noninferiority studies, while allowing patients every-8-week dosing
- The ULTOMIRIS safety profile was similar to that of eculizumab as observed in the largest phase 3 PNH clinical program
- ULTOMIRIS resulted in a reduction of free C5 levels in the blood, which was correlated with maximal intravascular hemolysis control in clinical studies
- ULTOMIRIS has weight-based dosing with 6-7 infusions per year[a]
- The serious adverse reactions in patients treated with ULTOMIRIS included hyperthermia and pyrexia

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[a]Starting 2 weeks after the initial loading dose, maintenance doses are administered once every 8 weeks.

[b]The mean (%CV) terminal elimination half-life and clearance of ravulizumab-cwvz in patients with PNH are 49.7 (18.0) days and 0.08 (29.5) L/day, respectively. Half-life of eculizumab is 11.25 to 17.25 days.

To learn more, visit www.ULTOMIRIS.com

Please see Important Safety Information throughout and on page 15. Please see accompanying full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.

ALEXION®