# ULTOMIRIS™ (RAVULIZUMAB-CWVZ)

## The First and Only Long-Acting C5 Complement Inhibitor for Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH)


See Important Safety Information for ULTOMIRIS™, including boxed warning regarding serious meningococcal infections, on page 4.

ULTOMIRIS™ (ravulizumab-cwvz) is the first and only approved long-acting C5 complement inhibitor for the treatment of PNH. In the largest-ever Phase 3 clinical studies in PNH, ULTOMIRIS met the high bar for efficacy and safety established by eculizumab and provided immediate and complete C5 inhibition that was sustained for a dosing interval of eight weeks, four times that of eculizumab.

### IMMEDIATE AND COMPLETE C5 COMPLEMENT INHIBITION FOR MAXIMAL HEMOLYSIS CONTROL

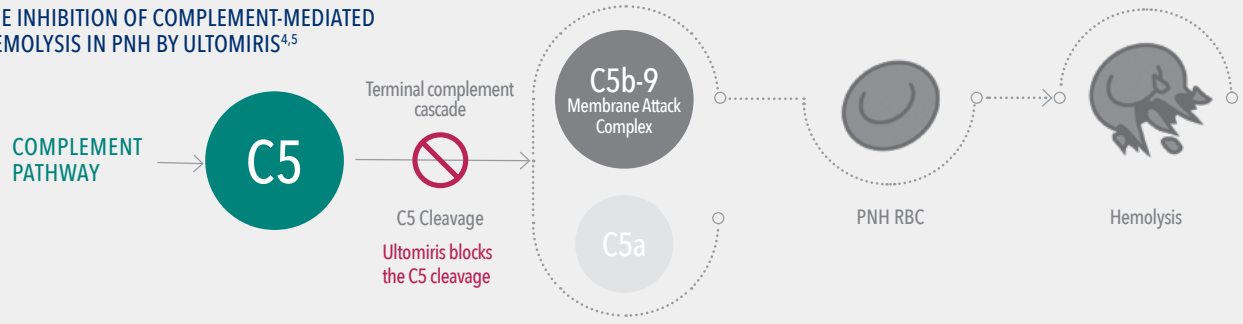
Paroxysmal nocturnal hemoglobinuria (PNH) is a chronic, progressive, debilitating and potentially life-threatening ultra-rare blood disorder characterized by complement-mediated hemolysis (destruction of red blood cells).[1,2] The red blood cells of patients with PNH are destroyed by the complement system, a part of the body's immune system, because they lack certain protective proteins.[3,4,5,6]

ULTOMIRIS provides maximal control of complement-mediated hemolysis in PNH by providing immediate and complete inhibition of the C5 protein in the terminal complement cascade (free C5 levels of <0.5 µg/mL).[7] Reduced hemolysis results in fewer thrombotic events, reduced need for transfusion, and improvements in fatigue and health-related quality of life.[7,8,9,10,11,12] Incomplete C5 inhibition can increase the risk of breakthrough hemolysis and related serious complications.[7,13,14,15]

### EXTENDED HALF-LIFE FOR SUSTAINED HEMOLYSIS CONTROL FOR EIGHT WEEKS

Targeted engineering enables ULTOMIRIS to use a natural pathway to escape degradation along with the captured C5 protein, and recycle back into the bloodstream while leaving C5 to degrade alone. This recycling results in a four-time longer half-life, which provided immediate and complete C5 inhibition and maximal hemolysis control that was sustained for eight weeks in clinical studies.[7,17,18,19,20] ULTOMIRIS is administered based on patients' body weight.

### THE INHIBITION OF COMPLEMENT-MEDIATED HEMOLYSIS IN PNH BY ULTOMIRIS[4,5]




An enzyme (C5 convertase) cleaves the C5 protein into the C5a and C5b proteins.

C5a is a potent anaphylatoxin, and amplifies coagulation. C5b initiates the assembly of the Membrane Attack Complex (MAC).[16,17,18]

Defective red blood cells (RBCs) in patients with PNH are not protected from complement attack, and lysis by the MAC.[16,17] Destroyed red blood cells release lactate dehydrogenase (LDH) and hemoglobin in the plasma.

Simplified, unscaled schema of cells. All steps and cell lines are not represented.

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## IN THE LARGEST PNH PHASE 3 CLINICAL PROGRAM, THE EFFICACY AND SAFETY PROFILE OF ULTOMIRIS WERE SIMILAR TO THAT OF ECULIZUMAB[7,17,19,20,21]

ULTOMIRIS was studied in the largest-ever Phase 3 PNH program, consisting of two non-inferiority studies with eculizumab that included patients who had either never been treated with a complement inhibitor before, or who had been on eculizumab treatment. The broad and clinically diverse patient populations were representative of PNH in clinical practice, including patients with various levels of disease activity, history of aplastic anemia and classic PNH, as well as transfused and non-transfused patients.

In these studies, the efficacy of ULTOMIRIS administered every eight weeks was non-inferior to the efficacy of eculizumab administered every two weeks based on all three primary endpoints. In the study with patients who had never been treated with a complement inhibitor, 73.6% of patients receiving ULTOMIRIS avoided transfusions, compared with 66.1% of patients receiving eculizumab. Lactate dehydrogenase (LDH) levels, a direct marker of hemolysis in PNH, were normalized in 53.6% of patients receiving ULTOMIRIS, compared with 49.4% of patients receiving eculizumab. In the study with patients who had been receiving eculizumab, a change in LDH levels from baseline of -0.82% was observed in the ULTOMIRIS group, compared with 8.39% in the eculizumab group (with a smaller value meaning less hemolysis).

### PHASE 3 EFFICACY RESULTS FOR ULTOMIRIS VS. ECULIZUMAB IN PATIENTS WITH PNH ACROSS PRIMARY AND KEY SECONDARY ENDPOINTS

| IN COMPLEMENT INHIBITOR-NAÏVE PATIENTS | Treatment Effect [95% CI: LB,UB] | | | Non-inferiority | |
|---|---|---|---|---|---|
| **Endpoint** | ULTOMIRIS n=125 | Eculizumab n=121 | Difference ULTOMIRIS vs. Eculizumab* | Pre-defined Requirement | Achieved* |
| **Primary** | | | | | |
| Patients avoiding transfusion [%] | 73.6% [65.9%,81.3%] | 66.1% [57.7%,74.6%] | 6.8% [-4.7%,18.1%][a] | LB > -20% | Yes |
| LDH normalization | 53.6% [45.9%,61.2%] | 49.4% [41.7%,57.0%] | 1.19 [0.80,1.77][b] | LB > 0.39 | Yes |
| **Secondary** | | | | | |
| Change in LDH levels | -76.8% [-80.0%,-73.7%] | -76.0% [-79.2%,-72.8%] | -0.83% [-5.2%,3.6%][c,†] | UB < 20% | Yes |
| Improvement in FACIT scale | 7.1 [5.6,8.6] | 6.4 [4.9,8.0] | 0.67 [-1.2,2.6][c] | LB > -5.0 | Yes |
| Patients with BTH [%] | 4.0% [0.6%,7.4%] | 10.7% [5.2%,16.3%] | -6.7% [-14.2%,0.18%][a,†] | UB < 20% | Yes |
| Patients with Hb stabilization [%] | 68.0% [59.8%,76.2%] | 64.5% [55.9%,73.0%] | 2.9% [-8.8%,14.6%][a] | LB > -20% | Yes |

| IN PATIENTS WHO HAD BEEN RECEIVING ECULIZUMAB | Treatment Effect [95% CI: LB,UB] | | | Non-inferiority | |
|---|---|---|---|---|---|
| **Endpoint** | ULTOMIRIS n=97 | Eculizumab n=98 | Difference ULTOMIRIS vs. Eculizumab* | Pre-defined Requirement | Achieved* |
| **Primary** | | | | | |
| Change in LDH levels [%] | -0.82 [-7.75, 6.11]† | 8.39 [1.47, 15.32] | -9.21 [-18.84, 0.42][c] | UB < 15 | Yes |
| **Secondary** | | | | | |
| Patients with BTH [%] | 0 [0.00, 3.73] | 5.1 [1.68, 11.51] | -5.1 [-18.99, 8.89][a] | UB < 20 | Yes |
| FACIT-Fatigue Scale | 2.0 [0.64, 3.39] | 0.5 [-0.84, 1.93] | 1.5 [-0.21, 3.15] | LB > -3 | Yes |
| Patients avoiding transfusion [%] | 87.6 [81.08, 94.18] | 82.7 [75.16, 90.15] | 5.5 [-4.27, 15.68][a] | LB > -20 | Yes |
| Patients with Hb stabilization [%] | 76.3 [67.82, 84.75] | 75.5 [67.00, 84.02] | 1.4 [-10.41, 13.31][a] | LB > -20 | Yes |

LDH: lactate dehydrogenase; FACIT: Functional Assessment of Chronic Illness Therapy; BTH: breakthrough hemolysis; Hb: hemoglobin; CI: confidence interval; LB: lower bound; UB: upper bound

*Non-inferiority is achieved if the LB or UB of the 95% CI of the treatment difference meets the pre-defined requirement

[a]Difference in proportion of patients; [b]Odds ratio; [c]Difference in change vs. Baseline

†Negative value meaning a stronger change in LDH levels or fewer events of breakthrough hemolysis

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Non-inferior efficacy to eculizumab was observed also on all eight key secondary endpoints, including the reduction of breakthrough hemolysis, a key secondary endpoint in both studies. In the study with patients who had never been treated with a complement inhibitor, breakthrough hemolysis was observed for 4.0% of patients in the ULTOMIRIS group, compared with 10.7% of patients in the eculizumab group. In the study with patients who had been receiving eculizumab, no patient receiving ULTOMIRIS experienced breakthrough, compared to five patients receiving eculizumab.

The safety profile of ULTOMIRIS was similar to that of eculizumab in these studies.

*See Important Safety Information for ULTOMIRIS, including boxed warning regarding serious meningococcal infections, on page 4.*

**PATIENTS WITH PNH EXPERIENCING BREAKTHROUGH HEMOLYSIS IN THE TWO PHASE 3 CLINICAL STUDIES OF ULTOMIRIS VS. ECULIZUMAB**

| | In complement inhibitor-naïve patients | | | In patients treated with Eculizumab before | | |
|---|---|---|---|---|---|---|
| | ULTOMIRIS n=125 | Eculizumab n=121 | Difference | ULTOMIRIS n=97 | Eculizumab n=98 | Difference |
| Patients with BTH (%) [95%CI] p value for non-inferiority | 5 (4.0) | 13 (10.7) | 8 (6.7) [-14.21, 0.18] p<0.0001 | 0 (0.0) | 5 (5.1) | -5 (-5.1) [-18.99, 8.89] p<0.0004 |
| BTH events \| patients | 5 \| 5 | 15 \| 13 | 10 \| 8 | 0 \| 0 | 7 \| 5 | 7 \| 5 |
| BTH events with incomplete C5 inhibition* | 0 | 7† | -7 | 0 | 4‡ | -4 |
| BTH events with infection (no incomplete C5 inhibition) | 4 | 4 | 0 | 0 | 2 | -2 |
| BTH events unrelated to incomplete C5 inhibition or infection§ | 1 | 4 | -3 | 0 | 1 | -1 |

BTH: Breakthrough hemolysis n: Total number of patients in the treatment group p-values represent

*Defined as free C5 serum concentration ≥0.5 µg/mL; §Undetermined cases had neither incomplete C5 inhibition nor concomitant infection identified to explain the cause of BTH; †Two patients in the eculizumab group with incomplete C5 inhibition also had concomitant infection; ‡One patient in the eculizumab group with incomplete C5 inhibition also had concomitant infection

## ABOUT THE CLINICAL STUDIES

The two non-inferiority, active-controlled, multi-national and multi-center, randomized open-label Phase 3 studies enrolled a total of 441 adult patients with PNH for a treatment duration of 26 weeks.

- *The first study enrolled 246 complement inhibitor-naïve patients and investigated transfusion avoidance and normalization of LDH levels as co-primary endpoints and percentage change from baseline in LDH levels, change from baseline in quality of life as assessed by the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale, proportion of patients with breakthrough hemolysis (BTH) and proportion of patients with stabilized hemoglobin levels as key secondary endpoints. BTH in the ULTOMIRIS group was not associated with incomplete C5 inhibition (mean serum concentrations of free C5 ≥0.5 µg/mL) compared to an association with incomplete C5 inhibition for seven of the 15 events of BTH in the eculizumab group. The most frequently observed adverse events (>10%) were headache, nasopharyngitis and upper respiratory tract infections. The most frequently observed serious adverse event was pyrexia.*[7,17,20,21]
- *The second study enrolled 195 patients who had been treated with eculizumab for at least the past six months in accordance with the U.S. Prescribing Information and investigated the change in LDH levels as primary endpoint and the proportion of patients with BTH, the change from baseline in quality of life as assessed by the FACIT- Fatigue scale, the proportion of patients avoiding transfusion, and the proportion of patients with stabilized hemoglobin levels as key secondary endpoints. No BTH was observed in the ULTOMIRIS group compared to seven BTH events in the eculizumab group (one patient experienced three events of BTH), four of which were associated with incomplete C5 inhibition (mean serum concentrations of free C5 ≥0.5 µg/mL). The most frequently observed adverse events (>10%) were upper respiratory infections, headache and cough. The most frequently observed serious adverse events were pyrexia and hemolysis.*[7,19,20,21]

## 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 [see Warnings and Precautions]. Enrollment in the ULTOMIRIS REMS program and additional information are available by telephone: 1-844-259-6783 or at www.ultomirisrems.com.**

## CONTRAINDICATIONS

ULTOMIRIS is contraindicated inpatients with unresolved *Neisseria meningitidis* infection.

## WARNINGS AND PRECAUTIONS

**Serious Meningococcal Infections**

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 for meningococcal disease according to the most current Advisory Committee on Immunization Practices (ACIP) recommendations for patients with complement deficiencies. Revaccinate patients in accordance with ACIP recommendations considering the duration of ULTOMIRIS therapy.

Immunize patients without a history of meningococcal vaccination at least 2 weeks prior to receiving the first dose of ULTOMIRIS. If urgent ULTOMIRIS therapy is indicated in an unvaccinated patient, administer meningococcal vaccine(s) as soon as possible and provide patients with 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.

Vaccination reduces, but does not eliminate, the risk of meningococcal infections. In 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.

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 steps to be taken to seek immediate medical care. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early. Consider discontinuation of ULTOMIRIS in patients who are undergoing treatment for serious meningococcal infection.

ULTOMIRIS REMS

Due to the risk of meningococcal infections, 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.

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.

Enrollment in the ULTOMIRIS REMS and additional information are available by telephone: 1-888-765-4747 or at **www.ultomirisrems.com**.

**Other Infections**

ULTOMIRIS blocks terminal complement activation; therefore patients may have increased susceptibility to encapsulated bacteria infections, especially infections caused by *Neisseria meningitis* but also *Streptococcus pneumoniae*, *Haemophilus influenzae*, and to a

lesser extent, *Neisseria gonorrhoeae*. If ULTOMIRIS therapy is administered to patients with active systemic infections, monitor closely for signs and symptoms of 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 ULTOMIRIS treatment has not been established. Therefore, treatment with ULTOMIRIS should not alter anticoagulant management.

**Infusion Reactions**

Administration of ULTOMIRIS may result in infusion reactions. In clinical trials, 3 out of 222 patients with PNH treated with ULTOMIRIS experienced infusion reactions (lower back pain, drop in blood pressure and infusion-related pain) during ULTOMIRIS administration. These reactions did not require discontinuation of ULTOMIRIS. Interrupt ULTOMIRIS infusion and institute appropriate 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%).

The serious adverse reactions in patients treated with ULTOMIRIS included hyperthermia and pyrexia.

**Please see full prescribing information for ULTOMIRIS, including Boxed WARNING, regarding serious and life-threatening meningococcal infections/sepsis.**

**References**


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