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

ULTOMIRIS is the first and only long-acting terminal complement inhibitor approved for both adult and pediatric patients with paroxysmal nocturnal hemoglobinuria (PNH)[1,2]

To reduce the risk of intravascular hemolysis, the driver of thrombosis[a] in PNH

BLOCK THE CAUSE

with immediate, complete, and sustained C5 inhibition.[1-11]

[a]Intravascular hemolysis, as measured by the biomarker LDH, is associated with a significantly increased risk of thromboembolic events in PNH.
C5=complement protein 5; LDH=lactate dehydrogenase.

UP TO
8
weeks control[b]

[b]Starting 2 weeks after the intravenous loading dose, maintenance doses are infused intravenously every 8 weeks for adult patients and every 4 or 8 weeks for pediatric patients (depending on body weight).

INDICATION

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

Subcutaneous Use in Adult Patients with PNH

Subcutaneous administration of ULTOMIRIS is not approved for use in pediatric patients.

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.**

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 REMS.

CONTRAINDICATIONS

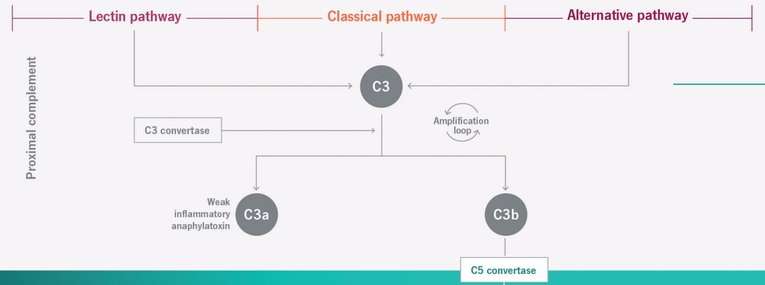
- Patients with unresolved *Neisseria meningitidis* infection.
- Patients who are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying ULTOMIRIS treatment outweigh the risks of developing a meningococcal infection.

Please see Important Safety Information throughout and accompanying full Prescribing Information (UltomirisHCP.com/PI) for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.

PNH is a chronic disease of devastating C5-mediated sequelae[7-10]

In PNH, an acquired *PIG-A* mutation in hematopoietic stem cells results in the complete or partial absence of the GPI-anchored proteins CD55 and CD59 from the surface of progeny cells, leading to complement-mediated intravascular hemolysis of affected RBCs, activation of other affected cells (platelets, WBCs), and **thrombosis, end-organ damage, and early mortality**.[7-10,12]

The complement cascade is a critical part of the normal innate immune response to pathogens[10,13-15]



C3-dependent immune activity[13-17]

- Microbial opsonization, leading to pathogen clearance
- Protection against severe infection by encapsulated bacteria, eg, *Haemophilus influenzae, Streptococcus pneumoniae,* and *Neisseria meningitidis*
- Immune complex clearance

C5-dependent immune activity[13,14,17]

- Direct pathogen lysis via the C5-mediated membrane attack complex (MAC)
- Protection against *Neisseria* (meningococcal and disseminated gonococcal infections)

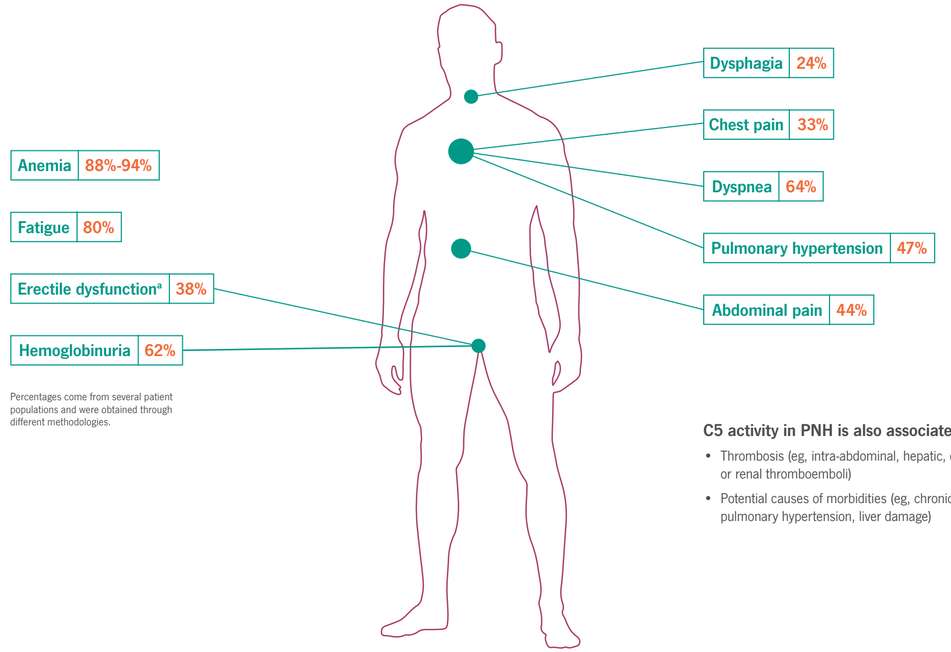
C5-dependent activity in PNH[10,12]

- Formation of MAC, leading to complement-mediated intravascular hemolysis (IVH) of PNH RBCs
- Platelet and WBC activation
- Creation of a prothrombotic environment

C3=complement protein 3; C5=complement protein 5; GPI=glycosylphosphatidylinositol; MAC=membrane attack complex; *PIG-A*=phosphatidylinositol glycan anchor biosynthesis class A; RBC=red blood cell; WBC=white blood cell.

C5 drives a wide range of unpredictable complications in PNH[18]

Comorbidities and consequences of C5-mediated IVH include[7,9,10,18-21]:



Percentages come from several patient populations and were obtained through different methodologies.

C5 activity in PNH is also associated with[7,8,10,12,21]:

- Thrombosis (eg, intra-abdominal, hepatic, cerebral, pulmonary, or renal thromboemboli)
- Potential causes of morbidities (eg, chronic kidney disease, pulmonary hypertension, liver damage)

[a]Male patients only (n=410).
C5=complement protein 5; IVH=intravascular hemolysis.

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

ULTOMIRIS targets C5 in the terminal complement[1]

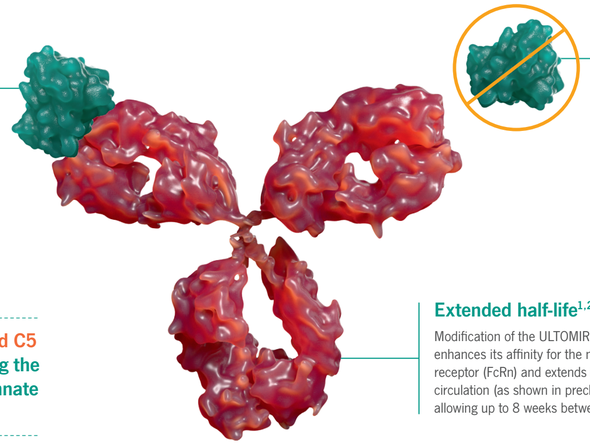
Built to block uncontrolled complement activity. Designed to preserve proximal complement–mediated immunity.[1-5,14]

ULTOMIRIS is the standard of care for PNH,[a] designed for extended C5 inhibition and elimination[1,22,23]

Pharmacology based on preclinical studies of ULTOMIRIS[22]

C5 inhibition[1,15]

ULTOMIRIS binds C5 with high affinity to give immediate, complete, and sustained C5 inhibition, without disrupting proximal complement immune activity.



C5 elimination[22,b]

Modifications to the Fab regions of ULTOMIRIS cause bound C5 to be released into the lysosome, where it is degraded.

Extended half-life[1,22,b-d]

Modification of the ULTOMIRIS Fc region enhances its affinity for the neonatal Fc receptor (FcRn) and extends its retention in circulation (as shown in preclinical models), allowing up to 8 weeks between infusions.

ULTOMIRIS is designed to provide sustained C5 inhibition and elimination without impacting the essential role of proximal complement in innate immune system activity[1,15,22]

[a]Based on US market share.
[b]Targeted engineering to incorporate 4 amino acid substitutions designed to reduce target-mediated drug disposition and enhance FcRn-mediated recycling of eculizumab led to the generation of ULTOMIRIS, which exhibited an extended duration of action in preclinical models relative to eculizumab.
[c]The mean (SD) terminal elimination half-life and clearance of intravenous ULTOMIRIS in patients with PNH are 49.6 (9.08) days and 0.08 (0.02) L/day, respectively. Half-life of eculizumab is 11.25 to 17.25 days.[1,23]
[d]Starting 2 weeks after the intravenous loading dose, maintenance doses are infused intravenously every 8 weeks for adult patients and every 4 or 8 weeks for pediatric patients (depending on body weight).
C5=complement protein 5; Fab=fragment antigen-binding; Fc=fragment crystallizable.

SELECT IMPORTANT SAFETY INFORMATION

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.

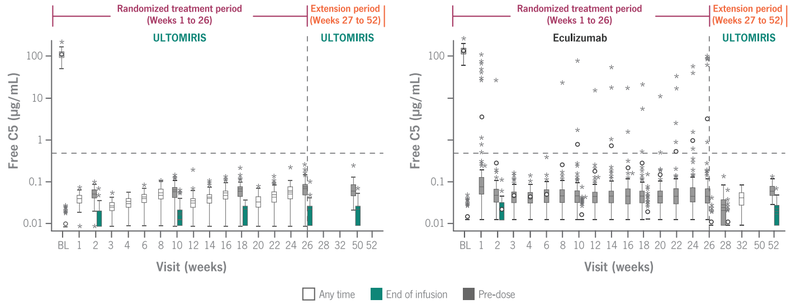
Vaccinate or revaccinate for meningococcal disease according to the most current ACIP recommendations for patients with complement deficiencies. Immunize patients without history of meningococcal vaccination at least 2 weeks prior to the first dose of ULTOMIRIS. Patients who initiate ULTOMIRIS treatment less than 2 weeks after receiving meningococcal vaccine(s) must receive appropriate prophylactic antibiotics until 2 weeks after vaccination.

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.

Please see Important Safety Information throughout and accompanying full Prescribing Information (UltomirisHCP.com/PI) for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.

ULTOMIRIS provided immediate, complete, and sustained C5 inhibition[1,2,4]

Mean free C5 levels over time in ULTOMIRIS- or eculizumab-treated adult patients with PNH who were complement inhibitor naïve[4,a-c]



[a]The horizontal line in the middle of each box indicates the median, and a diamond indicates the mean. The top and bottom borders of the box represent the 75th and 25th percentiles, respectively, and the whiskers represent the 1.5 interquartile range of the lower and upper portions of the quartile. Asterisks represent values outside the interquartile range. Dashed horizontal lines indicate serum free C5 concentration of 0.5 µg/mL.

Free C5 levels below 0.5 µg/mL were correlated with maximal intravascular hemolysis control and complete terminal complement inhibition in clinical studies[1]

[b]The complement inhibitor–naïve study (ALXN1210-PNH-301; NCT02946463) was a 26-week, multicenter, open-label, randomized, active-controlled, noninferiority, phase 3 study with an extension period. Adult patients (N=246) naïve to complement inhibitor treatment prior to study entry were randomized 1:1 to receive ULTOMIRIS or eculizumab. At the end of the randomized period, patients (N=243) entered the extension period, during which all received ULTOMIRIS.
[c]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 non-missing value before the first dose of study drug.
BL=baseline; C5=complement protein 5.

SELECT IMPORTANT SAFETY INFORMATION

Serious Meningococcal Infections (continued)

The benefits and risks of antibiotic prophylaxis for prevention of meningococcal infections in patients receiving ULTOMIRIS have not been established. In clinical studies with ULTOMIRIS, <1% of patients developed serious meningococcal infections/sepsis while receiving treatment with ULTOMIRIS. All were adult patients with PNH who had been vaccinated. These patients recovered while continuing treatment with ULTOMIRIS. Consider discontinuation of ULTOMIRIS in patients who are undergoing treatment for serious meningococcal infection.

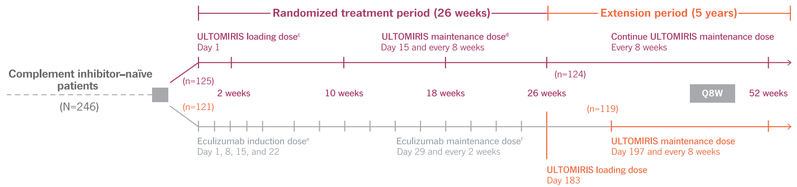
Please see Important Safety Information throughout and accompanying full Prescribing Information (UltomirisHCP.com/PI) for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.

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

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

ULTOMIRIS efficacy was evaluated in the largest clinical trial of adult patients with PNH to date[2,4]

This pivotal, phase 3, open-label, randomized, active-controlled, multicenter, noninferiority study included a broad, clinically diverse patient population of adults (≥18 years of age) with PNH who were complement inhibitor naïve (Study 301)[1,2,6,a,b]



Coprimary endpoints[1,2]
- Transfusion avoidance[g]
- LDH normalization

Secondary endpoints[2]
- Percent change from baseline in LDH levels
- Change in fatigue (FACIT-Fatigue)[h]
- Proportion of patients with breakthrough hemolysis[i]
- MAVEs[j]
- Proportion of patients with stabilized hemoglobin[k]

Baseline characteristics[1,2]	ULTOMIRIS (n=125)	Eculizumab (n=121)
Pretreatment LDH levels, median U/L (min, max)	1513.5 (378.0, 3759.5)	1445.0 (423.5, 3139.5)
Transfusion units in preceding 12 months, median (min, max)	6.0 (1, 44)	6.0 (1, 32)
Antithrombotic agent use in preceding 28 days, n (%)	22 (17.6)	22 (18.2)
Concomitant anticoagulant treatment, n (%)	23 (18.4)	28 (23.1)
History of MAVEs, n (%)	17 (13.6)	25 (20.7)
History of thrombosis, n (%)	17 (13.6)	20 (16.5)

- Disease characteristics were similar between study arms[2]
- Median pretreatment LDH levels were approximately 6x the upper limit of normal (246 U/L)[1,2]
- Patients received a median of 6 units of transfused packed RBCs or whole blood in the 12 months immediately preceding the study[l]

Over one-third of patients had a history of bone marrow failure disorders, including aplastic anemia (32%) and myelodysplastic syndrome (5%)[1]

[a]Population included male and female patients ≥18 years of age in 25 countries with diagnosis of PNH confirmed by red and white blood cell (granulocyte or monocyte) clone sizes of ≥5% by high-sensitivity flow cytometry.
[b]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]ULTOMIRIS weight-based loading dosing: ≥40 to <60 kg=2400 mg; ≥60 to <100 kg=2700 mg; ≥100 kg=3000 mg.
[d]ULTOMIRIS weight-based maintenance dosing: ≥40 to <60 kg=3000 mg; ≥60 to <100 kg=3300 mg; ≥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]FACIT-Fatigue scores can range from 0 to 52, with higher scores indicating less fatigue.
[i]Breakthrough hemolysis was defined as at least 1 new or worsening symptom or sign of intravascular hemolysis in the presence of elevated LDH ≥2 x ULN, after prior LDH reduction to <1.5 x ULN on therapy.
[j]MAVEs included both thromboembolisms (thrombophlebitis/deep vein thrombosis, renal vein thrombosis, renal arterial thrombosis, mesenteric/visceral vein thrombosis, mesenteric/visceral arterial thrombosis, hepatic/portal vein thrombosis, dermal thrombosis, acute peripheral vascular disease occlusion, cerebral arterial occlusion/cerebrovascular accident, cerebral venous occlusion, and pulmonary embolus) and nonthromboembolisms (amputation [nontraumatic, nondiabetic], myocardial infarction, transient ischemic attack, unstable angina, gangrene [nontraumatic, nondiabetic], and specified if other).
[k]Stabilized hemoglobin was defined as avoidance of a ≥2 g/dL decrease in hemoglobin level from baseline in the absence of transfusion.
FACIT=Functional Assessment of Chronic Illness Therapy; LDH=lactate dehydrogenase; MAVE=major adverse vascular event; Q8W=every 8 weeks; RBC=red blood cell; U/L=units per liter; ULN=upper limit of normal.

SELECT IMPORTANT SAFETY INFORMATION

ULTOMIRIS REMS

Due to the risk of meningococcal infections, ULTOMIRIS is available only through a restricted program under a REMS called ULTOMIRIS 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.

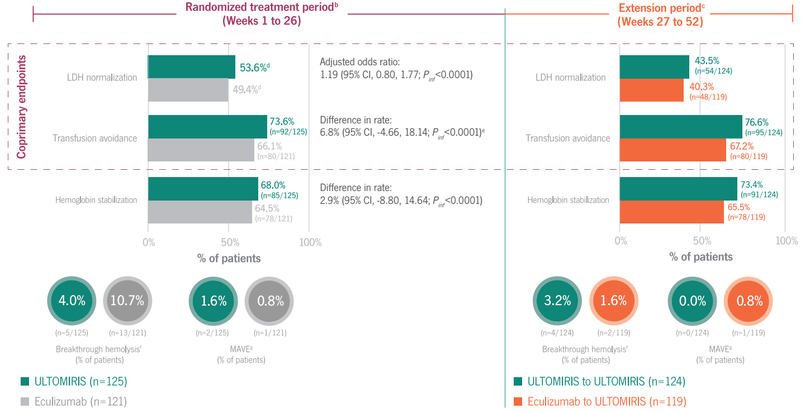
Additional information on the REMS requirements is available at www.ultomirisrems.com or 1-888-765-4747.

Please see Important Safety Information throughout and accompanying full Prescribing Information (UltomirisHCP.com/PI) 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

ULTOMIRIS every 8 weeks[a] demonstrated robust and sustained efficacy across all endpoints vs eculizumab in noninferiority studies[1,2]

Efficacy across primary and select secondary endpoints through 52 weeks of treatment[1,2,4]



- ULTOMIRIS was noninferior to eculizumab across all endpoints during the randomized treatment period (Week 0 to Week 26), including LDH normalization, transfusion avoidance, and hemoglobin stabilization[1,2]
- Among patients taking ULTOMIRIS in the randomized period, the prevalence of breakthrough hemolysis was 4.0%, and the prevalence of MAVEs was 1.6%[1,2,4]
- Efficacy in these measures was maintained through Week 52 of the extension period, during which all patients received ULTOMIRIS[4]
- At 2 years post baseline, 48.2% (108/224) of patients achieved LDH normalization[24]
- During months 12 through 18 of the extension period, transfusion avoidance was maintained in 73.3% (178/243) of patients and breakthrough hemolysis events were observed in 2.1% (5/243) of patients[24]

[a]Starting 2 weeks after the intravenous loading dose, maintenance doses are infused intravenously every 8 weeks for adult patients and every 4 or 8 weeks for pediatric patients (depending on body weight).
[b]Full analysis set (all patients who received ≥1 dose of study drug and had ≥1 efficacy assessment after the first infusion).
[c]Extension set (all patients who entered the extension period).
[d]For the LDH normalization endpoint during the randomized treatment period, the adjusted prevalence within each treatment is displayed.
[e]Treatment differences (95% CIs) are based on estimated differences in percent with 95% CI.
[f]Breakthrough hemolysis was defined as at least 1 new or worsening symptom or sign of intravascular hemolysis in the presence of elevated LDH ≥2 x ULN, after prior LDH reduction to <1.5 x ULN on therapy.
[g]MAVEs included both thromboembolisms (thrombophlebitis/deep vein thrombosis, renal vein thrombosis, renal arterial thrombosis, mesenteric/visceral vein thrombosis, mesenteric/visceral arterial thrombosis, hepatic/portal vein thrombosis, dermal thrombosis, acute peripheral vascular disease occlusion, cerebral arterial occlusion/cerebrovascular accident, cerebral venous occlusion, and pulmonary embolus) and nonthromboembolisms (amputation [nontraumatic, nondiabetic], myocardial infarction, transient ischemic attack, unstable angina, gangrene [nontraumatic, nondiabetic], and specified if other).
LDH=lactate dehydrogenase; MAVE=major adverse vascular event; ULN=upper limit of normal.

SELECT IMPORTANT SAFETY INFORMATION

Other Infections

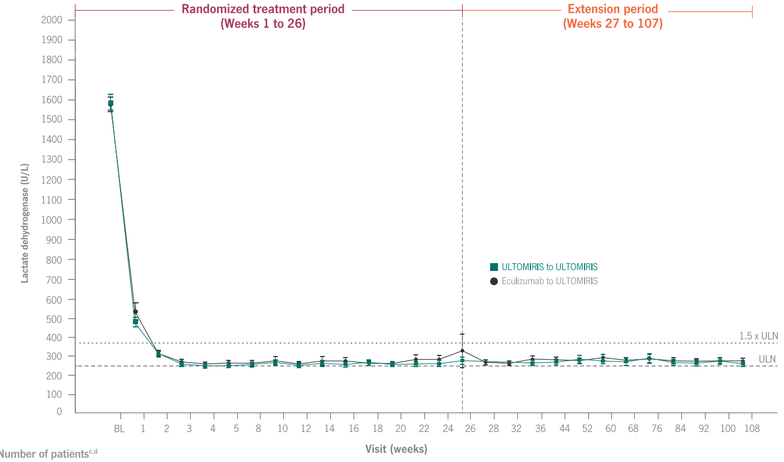
Patients may have increased susceptibility to infections, especially with encapsulated bacteria, such as infections caused by *Neisseria meningitidis* but also *Streptococcus pneumoniae*, *Haemophilus influenzae*, and to a lesser extent, *Neisseria gonorrhoeae*. Children treated with ULTOMIRIS may be 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.

Please see Important Safety Information throughout and accompanying full Prescribing Information (UltomirisHCP.com/PI) 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

ULTOMIRIS provided rapid and sustained control of LDH,[a] resulting in low rates of breakthrough hemolysis and MAVEs[4,24]

Mean LDH levels in complement inhibitor–naïve adult patients[4,24,b]



Number of patients[c,d]

	BL	1	2	3	4	5	8	10	12	14	16	18	20	22	24	26	28	32	36	44	52	60	68	76	84	92	100	108
ULTOMIRIS to ULTOMIRIS	124	119	123	122	123	123	124	123	122	123	123	120	124	123	122	123				124	122	121	120	121	119	120	119	116	115
Eculizumab to ULTOMIRIS	119	118	116	118	118	119	117	116	116	117	118	119	118	119	116	118	117	97	116	113	113	114	112	112	111	108	112	109

LDH is an established biomarker of intravascular hemolysis and PNH disease activity, with LDH levels ≥1.5 x ULN being associated with increased disease activity[7,8,25]

ULTOMIRIS treatment caused mean LDH levels to[1,2,4,24]:

- **Rapidly fall** below this 1.5 x ULN threshold by Week 2
- **Normalize** by Week 4
- **Be maintained** below 1.5 x ULN through 2 years

Through 1 year of ULTOMIRIS treatment[4,6]

95% (n=118/124) of patients were free of breakthrough hemolysis events[e]

98% (n=122/124) of patients were free of MAVEs

Through 2 years of ULTOMIRIS treatment[11]

In a post hoc analysis, incidence of MAVEs and thromboembolism was reduced compared to the 2 years preceding complement inhibitor treatment[f]

[a]In patients receiving ULTOMIRIS, LDH levels rapidly fell below 1.5 x ULN by Week 2, normalized by Week 4, and were maintained below 1.5 x ULN through Week 52.
[b]Error bars represent 95% CI.
[c]Number of patients may be lower than number enrolled at time point because of exclusion of samples having serum potassium ≥6 mmol/L and LDH ≥2 x ULN, missing samples (because of site error or for any other reason), or patient discontinuations during the extension.
[d]LDH levels were not measured for patients in the ULTOMIRIS to ULTOMIRIS group on Days 197 and 225.
[e]Breakthrough hemolysis was defined as at least 1 new or worsening symptom or sign of intravascular hemolysis in the presence of elevated LDH ≥2 x ULN, after prior LDH reduction to <1.5 x ULN on therapy.
[f]Based on post hoc analysis comparing the proportion of patients (N=244) experiencing a MAVE or thromboembolism in the 2 years prior to enrollment in the pivotal complement inhibitor–naïve study (Study 301) to the proportion after receiving ULTOMIRIS during 2 years of the study. Thromboembolisms included thrombophlebitis/deep vein thrombosis, renal vein thrombosis, renal arterial thrombosis, mesenteric/visceral vein thrombosis, mesenteric/visceral arterial thrombosis, hepatic/portal vein thrombosis, dermal thrombosis, acute peripheral vascular disease occlusion, cerebral arterial occlusion/cerebrovascular accident, cerebral venous occlusion, and pulmonary embolus. MAVEs included both thromboembolisms and nonthromboembolisms (amputation [nontraumatic, nondiabetic], myocardial infarction, transient ischemic attack, unstable angina, gangrene [nontraumatic, nondiabetic], and specified if other). MAVEs reported during the 2 years of treatment with ULTOMIRIS were all thromboembolisms.
BL=baseline; LDH=lactate dehydrogenase; MAVE=major adverse vascular event; U/L=units per liter; ULN=upper limit of normal.

SELECT IMPORTANT SAFETY INFORMATION

Monitoring Disease Manifestations after ULTOMIRIS Discontinuation

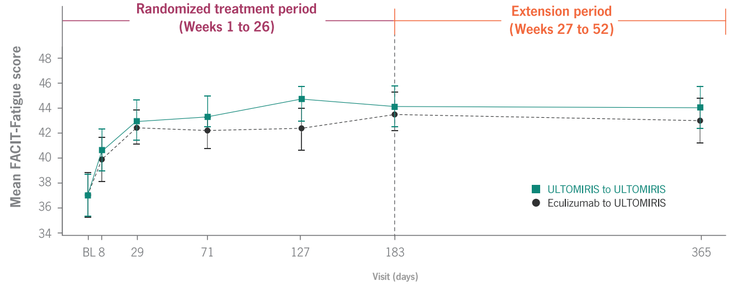
After discontinuing treatment with ULTOMIRIS, closely monitor for signs and symptoms of hemolysis, identified by elevated LDH along with sudden decrease in PNH clone size or hemoglobin, or re-appearance of symptoms such as fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), major 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.

Please see Important Safety Information throughout and accompanying full Prescribing Information (UltomirisHCP.com/PI) for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.

ULTOMIRIS improved and maintained FACIT-Fatigue scores[2,4,6]

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

Mean FACIT-Fatigue score in complement inhibitor–naïve adult patients[6,a]



Number of patients

	BL	8	29	71	127	183	365
ULTOMIRIS to ULTOMIRIS	124	119	124	124	124	124	118
Eculizumab to ULTOMIRIS	119	119	118	119	119	119	111

FACIT-Fatigue scores can range from 0 to 52, with higher scores indicating less fatigue[26]

The mean FACIT-Fatigue score for the general population has been estimated to be 43.5 (SD: 8.3)[26,b]

ULTOMIRIS provided a 7.07-point mean change in FACIT-Fatigue score at the end of the randomized period (95% CI, 5.55, 8.60; P_{inf} <0.0001) vs eculizumab[2,a]

This improvement in mean FACIT-Fatigue score was maintained through 2 years of treatment[4,6,24,a]

At 2 years post baseline

The mean FACIT-Fatigue score was 43.5 (SD: 8.10)[24]

[a]There was no observable difference in fatigue between ULTOMIRIS and eculizumab after 26 weeks of treatment compared to baseline as measured by the FACIT-Fatigue instrument. Patient-reported fatigue may be an underestimation or overestimation because patients were not blinded to treatment assignment.
[b]Mean FACIT-Fatigue score for the general population was determined through assessment of 2,426 adults (n=1,074 males; n=1,352 females; mean age [SD]: 49.8 [17.4] years) in Germany between March 2015 and May 2015.
BL=baseline; FACIT=Functional Assessment of Chronic Illness Therapy.

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

Intravenous or subcutaneous 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% of patients treated with ULTOMIRIS. These events included lower back pain, drop in blood pressure, elevation in blood pressure, limb discomfort, drug hypersensitivity (allergic reaction), dysgeusia (bad taste), and drowsiness. These reactions did not require discontinuation of ULTOMIRIS. If signs of cardiovascular instability or respiratory compromise occur, interrupt ULTOMIRIS infusion and institute appropriate supportive measures.

Please see Important Safety Information throughout and accompanying full Prescribing Information (UltomirisHCP.com/PI) 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

The safety of ULTOMIRIS was assessed in the largest phase 3 PNH clinical trial program to date[1,2,4,a,b]

Adverse reactions reported in 5% or more of adult patients treated with ULTOMIRIS during the 26-week randomized period[1]

Body system Adverse reaction	Number of patients	
	Eculizumab (n=219) n (%)	ULTOMIRIS (n=222) n (%)
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[c]	**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)

In the 26-week randomized period of the adult PNH clinical studies[1-3]:

- 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
- One patient receiving ULTOMIRIS discontinued treatment

[a]The complement inhibitor–naive study (ALXN1210-PNH-301; NCT02946463) was a 26-week, multicenter, open-label, randomized, active-controlled, noninferiority, phase 3 study with an extension period. Adult patients (N=246) naive to complement inhibitor treatment prior to study entry were randomized 1:1 to receive ULTOMIRIS or eculizumab. At the end of the randomized period, patients (N=243) entered the extension period, during which all received ULTOMIRIS.
[b]The ULTOMIRIS switch study (ALXN1210-PNH-302; NCT03056040) was a 26-week, multicenter, open-label, randomized, active-controlled, noninferiority, phase 3 study with an extension period. Adult patients (N=195) who were clinically stable after having been treated with eculizumab for at least the past 6 months were randomized 1:1 to either continue eculizumab or to switch to ULTOMIRIS. At the end of the randomized period, patients (N=191) entered the extension period during which all received ULTOMIRIS.
[c]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.

Please see Important Safety Information throughout and accompanying full Prescribing Information (UltomirisHCP.com/PI) for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.

No new safety signals were reported through 2 years of ULTOMIRIS treatment[24]

Intravenous ULTOMIRIS safety outcomes reported from Week 27 to 2 years of treatment in the safety population (N=434)[24]

Type of adverse event Adverse reaction	Number (%) of patients
Any TEAE[a]	**391** (90.1)
TEAE considered as a MAVE	**6** (1.4)[b]
Most common TEAEs (occurring in ≥10% of patients)	
Upper respiratory tract infection	**80** (18.4)
Nasopharyngitis	**70** (16.1)
Headache	**56** (12.9)
Pyrexia	**44** (10.1)
Any SAE	**86** (19.8)
SAE leading to study drug discontinuation	**3** (0.7)[c]
Death	**4** (0.9)[d]

[a]TEAEs are AEs with a start date and start time on or after the date and time of the first infusion of ULTOMIRIS.
[b]Eight MAVEs were recorded; 1 patient had 2 events of pulmonary embolism, 1 patient had 2 events of cerebral infarction. The other MAVEs included thrombophlebitis, deep vein thrombosis, jugular vein thrombosis, and peripheral artery thrombosis. Six events were considered to be unrelated to treatment, and 2 events were unlikely related to treatment. None of these events led to change in dose.
[c]The 3 recorded discontinuations were due to acute myeloid leukemia, myelodysplastic syndrome, and lung adenocarcinoma.
[d]Four deaths unrelated to ULTOMIRIS were reported and were due to pulmonary sepsis, acute myeloid leukemia, lung adenocarcinoma, and lung neoplasm malignant. The 2 deaths leading to study drug discontinuation were due to acute myeloid leukemia and lung adenocarcinoma.

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 at 1-888-765-4747 or at UltomirisREMS.com.

AE=adverse event; C5=complement protein 5; MAVE=major adverse vascular event; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

Please see Important Safety Information throughout and accompanying full Prescribing Information (UltomirisHCP.com/PI) 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

inhibitors have an established safety profile in the more than

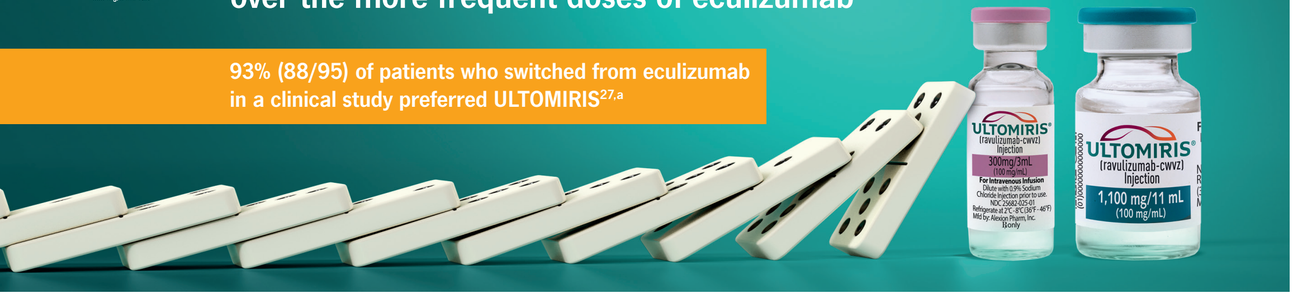
30,000 patients

who have been treated with ULTOMIRIS and eculizumab to date[6]

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

Patients prefer the less frequent doses of ULTOMIRIS over the more frequent doses of eculizumab[27]

93% (88/95) of patients who switched from eculizumab in a clinical study preferred ULTOMIRIS[27,a]



Recommended vaccinations

- 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

ULTOMIRIS requires as few as 6 or 7 infusions per year[1,b]

<1 HOUR

For most patients, ULTOMIRIS can be infused in less than an hour[1-3,c]

UP TO **8** weeks

ULTOMIRIS is infused intravenously every 4 or 8 weeks,[b] giving patients freedom and flexibility between treatments[1,27]

[a]In substudy ALXN1210-PNH-302s, 95 patients enrolled in the extension period of the ULTOMIRIS switch study (ALXN1210-PNH-302; NCT03056040) completed the Paroxysmal Nocturnal Hemoglobinuria Patient Preference Questionnaire (PNH-PPQ®) to report on their overall treatment preference and the treatment characteristics that were most important to that preference.
[b]Starting 2 weeks after the intravenous loading dose, maintenance doses are infused intravenously every 8 weeks for adult patients and every 4 or 8 weeks for pediatric patients (depending on body weight).

[c]The mean (SD) weights for patients in Study 301 (N=246) and Study 302 (N=195) were 68.7 kg (15.2) and 72.9 kg (15.7), respectively. For patients weighing 60 kg to <100 kg, minimum loading dose infusion time is 0.6 hours and minimum maintenance dose infusion time is 0.7 hours.
ACIP=Advisory Committee on Immunization Practices.

SELECT IMPORTANT SAFETY INFORMATION

Injection Site Reactions-Subcutaneous administration

27% (23/84) of patients treated with subcutaneous administration of ULTOMIRIS experienced injection site reactions which included application site rash, device allergy, infusion site pain, infusion site reaction, injection site bruising, injection site erythema, injection site hematoma, injection site induration, injection site inflammation, injection site pain, injection site pruritus, injection site rash, injection site reaction, injection site swelling, injection site urticaria, medical device site bruise, medical device site erythema, medical device site hematoma, medical device site induration, medical device site pruritus, medical device site rash, and medical device site reaction.

Allergies to Acrylic Adhesives

The on-body injector of ULTOMIRIS uses acrylic adhesive. For patients with a known allergy to acrylic adhesive, use of this product may result in an allergic reaction. Premedication can be considered, and supportive measures should be instituted if signs of allergy appear.

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.

Please see Important Safety Information throughout and accompanying full Prescribing Information (UltomirisHCP.com/PI) for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.

Determining the ULTOMIRIS dose and schedule

The recommended weight-based dosing regimen consists of a loading dose followed by maintenance doses.

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

Patients starting ULTOMIRIS with no prior treatment

ULTOMIRIS loading dose — **ULTOMIRIS** maintenance doses

2 weeks — Every 4 or 8 weeks (depending on body weight)

Starting 2 weeks after the intravenous loading dose, maintenance doses are infused intravenously **once every 4 or 8 weeks (depending on body weight)**.

Patients switching from eculizumab to ULTOMIRIS

Last eculizumab infusion — **ULTOMIRIS** loading dose — **ULTOMIRIS** maintenance doses

At time of next scheduled eculizumab dose — Every 4 or 8 weeks (depending on body weight)

Loading dose of ULTOMIRIS should be infused intravenously at the time of the next scheduled eculizumab dose. Maintenance doses are infused intravenously once every **4 or 8 weeks (depending on body weight), starting 2 weeks after the loading dose**.

Weight-based dosing regimen[a]

Body weight range (kg)[b]	Loading dose (mg)	Maintenance dose (mg) and dosing interval	
5 to <10	600	300	Every 4 weeks
10 to <20	600	600	
20 to <30	900	2,100	Every 8 weeks
30 to <40	1,200	2,700	
40 to <60	2,400	3,000	
60 to <100	2,700	3,300	
100 or greater	3,000	3,600	

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.

[a]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.
[b]Body weight at time of treatment.
LDH=lactate dehydrogenase.

SELECT IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS (continued)

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%).

Adverse Reactions for Subcutaneous Administration of ULTOMIRIS

Most common adverse reactions (≥10%) with ULTOMIRIS subcutaneous administration via On Body Injector in adult patients with PNH were local injection site reactions, diarrhea, and headache.

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.

Please see Important Safety Information throughout and accompanying full Prescribing Information (UltomirisHCP.com/PI) for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.

ONESOURCE®
Personalized Patient Support from Alexion

OneSource™ is here to help

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

$0 in out-of-pocket costs for eligible patients[a,b]

Copay assistance

- **The Alexion OneSource CoPay Program provides financial assistance by covering eligible patients' out-of-pocket medication and infusion costs associated with ULTOMIRIS up to $15,000 US dollars per calendar year**
- Valid only for patients with commercial insurance who have a valid prescription for a US FDA–approved indication of ULTOMIRIS. Not valid for patients covered by government insurance programs[c] or other federal or state programs (including any state prescription drug assistance programs)
- Additional requirements may apply. Contact Alexion OneSource for more information on patient eligibility

Alexion Patient Liaisons and Patient Navigators 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 navigation

- 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

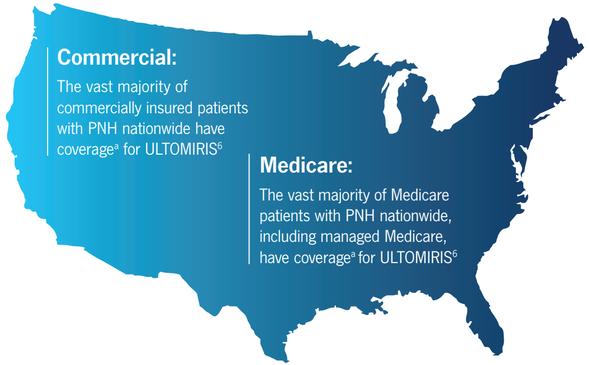
- Providing information to patients regarding in-person and online meetings and events
- Connecting patients with other people living with PNH

[a]Based on typical commercial patient out-of-pocket deductible limits.
[b]Additional terms and conditions apply. Please contact OneSource with additional questions.
[c]Includes Medicaid, Medicare (including Medicare Part D), Medicare Advantage Plans, Medigap, Veterans Affairs, Department of Defense, or TRICARE. Patients residing in Massachusetts or Rhode Island are eligible for assistance with medication costs but are not eligible for assistance with infusion costs.

Please see Important Safety Information throughout and accompanying full Prescribing Information (UltomirisHCP.com/PI) 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

ULTOMIRIS is covered[a] for PNH by virtually every health plan nationwide[6]



ALEXION ACCESS NAVIGATOR

OneSource™ Patient Navigators and Patient Liaisons help assist with health insurance information.

91.3% of patients with PNH enrolled in OneSource initiate ULTOMIRIS treatment within 30 days of enrollment (n=138)[6,b]

Average time to ULTOMIRIS treatment initiation was 7.1 days for patients with PNH consented in OneSource (n=81)[6,b]

[a]The payer policy allows for use of ULTOMIRIS, usually under the medical benefit.
[b]Includes patients with PNH enrolled in OneSource from 12/1/2020 to 5/31/2021.

References:

1. ULTOMIRIS. Prescribing information. Alexion Pharmaceuticals, Inc. **2.** Lee JW, Sicre de Fontbrune F, Wong Lee Lee L, et al. *Blood.* 2019;133(6):530-539. **3.** Kulasekararaj AG, Hill A, Rottinghaus ST, et al. *Blood.* 2019;133(6):540-549. **4.** Schrezenmeier H, Kulasekararaj A, Mitchell L, et al. *Ther Adv Hematol.* 2020;11:2040620720966137. **5.** Kulasekararaj AG, Hill A, Langemeijer S, et al. *Eur J Haematol.* 2021;106(3):389-397. **6.** Data on file. Alexion Pharmaceuticals, Inc. **7.** Lee JW, Jang JH, Kim JS, et al. *Int J Hematol.* 2013;97(6):749-757. **8.** Jang JH, Kim JS, Yoon SS, et al. *J Korean Med Sci.* 2016;31(2):214-221. **9.** Rother RP, Bell L, Hillmen P, Gladwin MT. *JAMA.* 2005;293(13):1653-1662. **10.** Brodsky RA. *Blood.* 2014;124(18):2804-2811. **11.** Peffault de Latour R, Hill A, Füreder W, et al. e-Poster presented at: European Hematology Association 26th Congress; June 9-17, 2021. **12.** Hill A, DeZern AE, Kinoshita T, Brodsky RA. *Nat Rev Dis Primers.* 2017;3:17028. **13.** Murphy K. *Janeway's Immunobiology.* 8th ed. Garland Science, Taylor & Francis Group LLC; 2012:37-71. **14.** Walport MJ. *N Engl J Med.* 2001;344(14):1058-1066. **15.** Kelly R, Richards S, Hillmen P, Hill A. *Ther Clin Risk Manag.* 2009;5:911-921. **16.** Figueroa JE, Densen P. *Clin Microbiol Rev.* 1991;4(3):359-395. **17.** Ram S, Lewis LA, Rice PA. *Clin Microbiol Rev.* 2010;23(4):740-780. **18.** Schrezenmeier H, Röth A, Araten DJ, et al. *Ann Hematol.* 2020;99(7):1505-1514. **19.** Nishimura JI, Kanakura Y, Ware RE, et al. *Medicine.* 2004;83(3):193-207. **20.** Hill A, Rother RP, Wang X, et al. *Br J Haematol.* 2010;149(3):414-425. **21.** Bessler M, Hiken J. *Hematology Am Soc Hematol Educ Program.* 2008;104-110. **22.** Sheridan D, Yu ZX, Zhang Y, et al. *PLoS One.* 2018;13(4):e0195909. **23.** SOLIRIS. Prescribing information. Alexion Pharmaceuticals, Inc. **24.** Kulasekararaj AG, Griffin M, Langemeijer S, et al. *Eur J Haematol.* 2022;109(3):205-214. **25.** Schrezenmeier H, Muus P, Socié G, et al. *Haematologica.* 2014;99(5):922-929. **26.** Montan I, Löwe B, Cella D, Mehnert A, Hinz A. *Value Health.* 2018;21(11):1313-1321. **27.** Peipert JD, Kulasekararaj AG, Gaya A, et al. *PLoS One.* 2020;15(9):e0237497.

Please see Important Safety Information throughout and accompanying full Prescribing Information (UltomirisHCP.com/PI) 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

For more information, please visit:

AlexionOneSource.com

UltomirisHCP.com

UltomirisREMS.com

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

The standard of care[a] for adult patients with PNH is FDA approved for pediatric patients[1,6]

To reduce the risk of intravascular hemolysis, the driver of thrombosis in PNH[1-11,b]

BLOCK THE CAUSE

ULTOMIRIS, administered every 8 weeks,[c] is the standard of care[a] for PNH in adults[1,6]

- **Immediate, complete, and sustained C5 inhibition with ULTOMIRIS[1,2,4]**
- **ULTOMIRIS provided rapid and sustained control of LDH[1,2,4,d]**
- **>30,000 patients have been treated with ULTOMIRIS and eculizumab** to date, establishing the safety profile of C5 inhibitors[6]
- **No new safety signals reported through 2 years of treatment[24]**
- In the pivotal clinical trials, the most common adverse reactions (incidence ≥10%) were upper respiratory tract infection and headache[1]
- ULTOMIRIS is covered[e] for PNH by **virtually every health plan nationwide[6]**

[a]Based on US market share.
[b]Intravascular hemolysis, as measured by the biomarker LDH, is associated with a significantly increased risk of thromboembolic events in PNH.
[c]Starting 2 weeks after the intravenous loading dose, maintenance doses are infused intravenously every 8 weeks for adult patients and every 4 or 8 weeks for pediatric patients (depending on body weight).
[d]In patients receiving ULTOMIRIS, LDH levels rapidly fell below 1.5 x ULN by Week 2, normalized by Week 4, and were maintained below 1.5 x ULN through Week 52.
[e]The payer policy allows for use of ULTOMIRIS, usually under the medical benefit.
C5=complement protein 5; LDH=lactate dehydrogenase; ULN=upper limit of normal.

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.**

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 REMS.

To learn more, visit BlockTheCause.com

Please see Important Safety Information throughout and accompanying full Prescribing Information (UltomirisHCP.com/PI) for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.

ALEXION®
AstraZeneca Rare Disease