

#1 PRESCRIBED
TREATMENT
for
atypical-HUS^{1,2*}

Consider a treatment used for more than 1,000 patients with atypical-HUS,^{1†} and more than 9,000 patient-years across all ULTOMIRIS indications^{3‡}

ULTOMIRIS[®]
(ravulizumab-cwvz)

Immediate, complete, and sustained[§] C5 inhibition with ULTOMIRIS in adult and pediatric patients with atypical-HUS^{2,4,5}

SELECT IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

ULTOMIRIS, a complement inhibitor, increases the risk of serious infections caused by *Neisseria meningitidis* [see Warnings and Precautions (5.1)] Life-threatening and fatal meningococcal infections have occurred in patients treated with complement inhibitors. These infections may become rapidly life-threatening or fatal if not recognized and treated early.

- Complete or update vaccination for meningococcal bacteria (for serogroups A, C, W, Y, and B) at least 2 weeks prior to the first dose of ULTOMIRIS, unless the risks of delaying ULTOMIRIS therapy outweigh the risk of developing a serious infection. Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against meningococcal bacteria in patients receiving a complement inhibitor. See Warnings and Precautions (5.1) for additional guidance on the management of the risk of serious infections caused by meningococcal bacteria.
- Patients receiving ULTOMIRIS are at increased risk for invasive disease caused by *Neisseria meningitidis*, even if they develop antibodies following vaccination. Monitor patients for early signs and symptoms of serious meningococcal infections and evaluate immediately if infection is suspected.

Because of the risk of serious meningococcal infections, ULTOMIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called ULTOMIRIS and SOLIRIS REMS [see Warnings and Precautions (5.2)].

INDICATION

ULTOMIRIS is indicated for the treatment of adult and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA).

Limitation of Use:

ULTOMIRIS is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

SELECT IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- Initiation in patients with unresolved serious *Neisseria meningitidis* infection.

WARNINGS AND PRECAUTIONS

Serious Meningococcal Infections

ULTOMIRIS, a complement inhibitor, increases a patient's susceptibility to serious, life-threatening, or fatal infections caused by meningococcal bacteria (septicemia and/or meningitis) in any serogroup, including non-groupable strains. Life-threatening and fatal meningococcal infections have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors.

Revaccinate patients in accordance with ACIP recommendations considering the duration of ULTOMIRIS therapy. Note that ACIP recommends an administration schedule in patients receiving complement inhibitors that differs from the administration schedule in the vaccine prescribing information. If urgent ULTOMIRIS therapy is indicated in a patient who is not up to

date with meningococcal vaccines according to ACIP recommendations, provide antibacterial drug prophylaxis and administer meningococcal vaccines as soon as possible. Various durations and regimens of antibacterial drug prophylaxis have been considered, but the optimal durations and drug regimens for prophylaxis and their efficacy have not been studied in unvaccinated or vaccinated patients receiving complement inhibitors, including ULTOMIRIS. The benefits and risks of treatment with ULTOMIRIS, as well as those associated with antibacterial drug prophylaxis in unvaccinated or vaccinated patients, must be considered against the known risks for serious infections caused by *Neisseria meningitidis*.

Vaccination does not eliminate the risk of serious meningococcal infections, despite development of antibodies following vaccination.

Closely monitor patients for early signs and symptoms of meningococcal infection and evaluate patients immediately if infection is suspected. Inform patients of these signs and symptoms and instruct patients to seek immediate medical care if they occur. Promptly treat known infections. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early. Consider interruption of ULTOMIRIS in patients who are undergoing treatment for serious meningococcal infection depending on the risks of interrupting treatment in the disease being treated.

ULTOMIRIS and SOLIRIS REMS

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

*ULTOMIRIS had more than a 50% share of patients with atypical-HUS actively taking Alexion medications every month from August 2021 through August 2023.¹

[†]Reflects the number of patients with atypical-HUS currently on ULTOMIRIS as of August 2023.¹

[‡]Based on a cumulative search of the Alexion safety database for real-world ravulizumab data from December 2018 to December 2022 across all indications.³ See all indications at UltomirisHCP.com.

[§]In the majority (93%) of adult and pediatric patients with atypical-HUS throughout the entire 26-week treatment period.²

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

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

ULTOMIRIS IS THE FIRST AND ONLY C5 INHIBITOR FOR ATYPICAL-HUS LASTING UP TO 8 WEEKS²

For adult and pediatric patients 1 month of age and older with atypical-HUS to inhibit complement-mediated TMA^{2*}

IMMEDIATE

100% (n=70) of adult and pediatric patients had complete C5 inhibition at the end of the first infusion of ULTOMIRIS.^{2,4-6}

COMPLETE

54% (n=30/56; 95% CI: 40%-67%) of adult and 71% (n=10/14; 95% CI: 42%-92%) of pediatric patients met the composite endpoint of complete TMA response with ULTOMIRIS by 26 weeks.^{2†‡} Four additional adult patients who did not achieve a complete TMA response at 26 weeks did so with continued ULTOMIRIS treatment at 52 weeks.^{2,6}

SUSTAINED

Up to 8 weeks of sustained C5 inhibition and the possibility to live dialysis-free in adult and pediatric patients.^{2§}

ULTOMIRIS has a minimum treatment duration of 6 months; treatment beyond 6 months should be individualized per each patient's need²

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). For patients transitioning from SOLIRIS[®] (eculizumab), administer the loading dose of ULTOMIRIS at the time of the next scheduled SOLIRIS dose.

ULTOMIRIS treatment of atypical-HUS should be a minimum duration of 6 months

- Due to the heterogeneous nature of atypical-HUS events and patient-specific risk factors, treatment duration beyond the initial 6 months should be individualized
- If the patient discontinues treatment with ULTOMIRIS, patients should be monitored for clinical symptoms and laboratory signs of TMA complications for at least 12 months
- There are no specific data on ULTOMIRIS discontinuation

*Limitation of Use: ULTOMIRIS is not indicated for the treatment of patients with STEC-HUS.²

†Complete TMA response was defined as normalization of hematological parameters (platelet count and LDH) and $\geq 25\%$ improvement in serum creatinine from baseline during the 26-week initial evaluation period. Patients had to meet all criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart and any measurement in between.²

‡Interim results of a 26-week, multicenter, open-label, single-arm study of 14 SOLIRIS-naïve patients with documented diagnosis of atypical-HUS.²

§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).²

C5=complement protein 5; LDH=lactate dehydrogenase; STEC-HUS=Shiga toxin *E. coli*-related hemolytic uremic syndrome; TMA=thrombotic microangiopathy.

SELECT IMPORTANT SAFETY INFORMATION (continued)

ULTOMIRIS and SOLIRIS REMS (continued)

Prescribers must enroll in the REMS, counsel patients about the risk of serious meningococcal infection, provide patients with the REMS educational materials, assess patient vaccination status for meningococcal vaccines (against serogroups A, C, W, Y, and B) and vaccinate if needed according to current ACIP recommendations two weeks prior to the first dose of ULTOMIRIS. Antibacterial drug prophylaxis must be prescribed if treatment must be started urgently, and the patient is not up to date with both meningococcal vaccines according to current ACIP recommendations at least two weeks prior to the first dose of ULTOMIRIS. Patients must receive counseling about the need to receive meningococcal vaccines and to take antibiotics as directed, signs and symptoms of meningococcal infection, and be instructed to carry the Patient Safety Card at all times during and for 8 months following ULTOMIRIS treatment.

Further information is available at www.UltSolREMS.com or 1-888-765-4747.

Other Infections

Serious infections with *Neisseria* species (other than *Neisseria meningitidis*), including disseminated gonococcal infections, have been reported.

ULTOMIRIS blocks terminal complement activation; therefore, patients may have increased susceptibility to infections, especially with encapsulated bacteria, such as infections caused by *Neisseria meningitidis* but also *Streptococcus pneumoniae*, *Haemophilus influenzae*, and to a lesser extent, *Neisseria gonorrhoeae*. Children treated with ULTOMIRIS may be at increased risk of developing serious infections due to *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib). Administer vaccinations for the prevention of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) infections according to ACIP recommendations. Patients receiving ULTOMIRIS are at increased risk for infections due to these organisms, even if they develop antibodies following vaccination.

Monitoring Disease Manifestations after ULTOMIRIS Discontinuation

ULTOMIRIS treatment of aHUS should be a minimum duration of 6 months. Due to heterogeneous nature of aHUS events and patient-specific risk factors, treatment duration beyond the initial 6 months should be individualized. There are no specific data on ULTOMIRIS discontinuation. After discontinuing treatment with ULTOMIRIS, patients should be monitored for clinical symptoms and laboratory signs of TMA complications for at least 12 months. TMA complications post-discontinuation can be identified if any of the following is observed: Clinical symptoms of TMA include changes in mental status, seizures, angina, dyspnea, thrombosis or increasing blood pressure. In addition, at least two of the following laboratory signs observed concurrently and results should be confirmed by a second measurement 28 days apart with no interruption: a decrease in platelet count of 25% or more as compared to either baseline or to peak platelet count during ULTOMIRIS treatment; an increase in serum creatinine of 25% or more as compared to baseline or to nadir during ULTOMIRIS treatment; or, an increase in serum LDH of 25% or more as compared to baseline or to nadir during ULTOMIRIS treatment. If TMA complications occur after discontinuation, consider reinitiation of ULTOMIRIS treatment or appropriate organ-specific supportive measures.

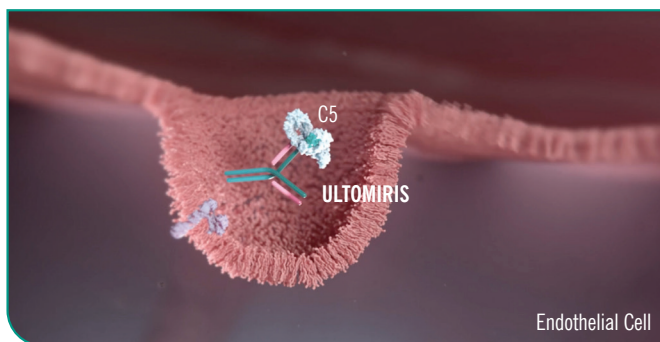

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(ravulizumab-cwvz)
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300 mg/3 mL vial

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

ULTOMIRIS BINDS TO C5 FOR IMMEDIATE, COMPLETE, AND SUSTAINED C5 INHIBITION

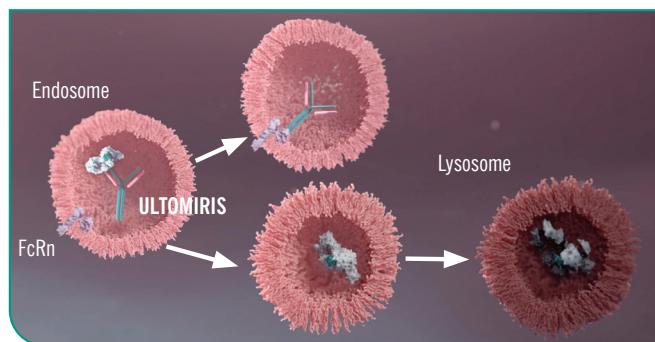
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ULTOMIRIS binds to C5 in the bloodstream to prevent its activation.²



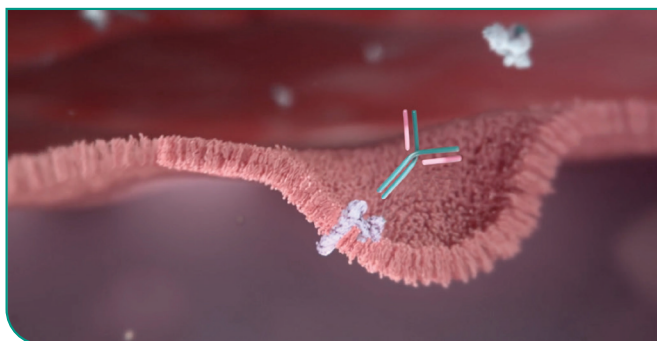
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ULTOMIRIS is engineered to release C5 in the endosome as pH levels drop and use FcRn to recycle back to the bloodstream, leaving C5 to be degraded by the lysosome.⁷



3

ULTOMIRIS has also been engineered to bind to FcRn to provide immediate, complete, and sustained* inhibition of C5 for up to 8 weeks.^{2,6,7}



SELECT IMPORTANT SAFETY INFORMATION (continued)

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 administration may result in systemic infusion-related reactions, including anaphylaxis and hypersensitivity reactions. In clinical trials, infusion-related reactions occurred in approximately 1 to 7% of patients treated with ULTOMIRIS. These events included lower back pain, drop 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.

ADVERSE REACTIONS

Most common adverse reactions in patients with aHUS (incidence $\geq 20\%$) were upper respiratory tract infection, diarrhea, nausea, vomiting, headache, hypertension and pyrexia. Serious adverse reactions were reported in 42 (57%) patients with aHUS receiving ULTOMIRIS. The most frequent serious adverse reactions reported in more than 2 patients (2.7%) treated with ULTOMIRIS were hypertension, pneumonia and abdominal pain.

Adverse reactions reported in $\geq 20\%$ of pediatric patients treated with ULTOMIRIS were diarrhea, constipation, vomiting, pyrexia, upper respiratory tract infection, decreased vitamin D, headache, cough, rash, and hypertension.

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.

To report SUSPECTED ADVERSE REACTIONS, contact Alexion Pharmaceuticals, Inc. at 1-844-259-6783 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

*In the majority (93%) of adult and pediatric patients with atypical-HUS throughout the entire 26-week treatment period.²
FcRn=neonatal Fc receptor.

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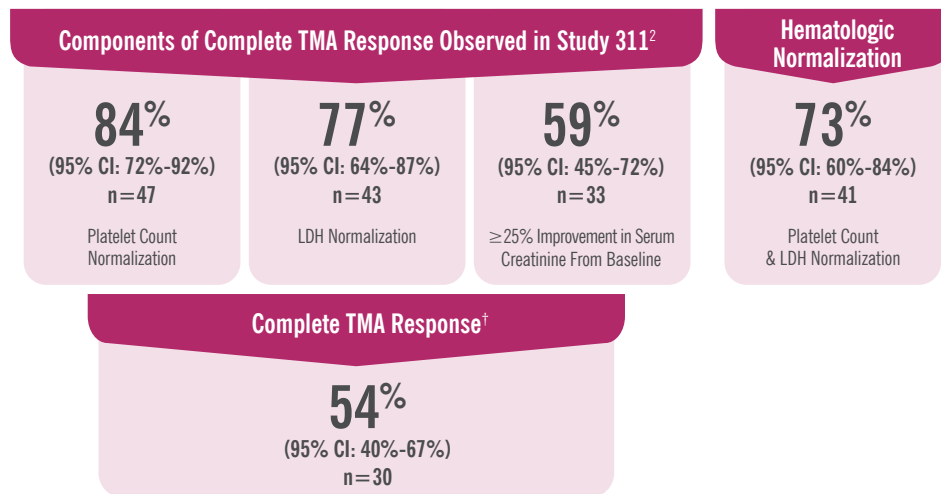
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STUDY 311: ULTOMIRIS IN ADULT PATIENTS WITH ATYPICAL-HUS

IMMEDIATE C5 inhibition was observed on Day 1 in adult patients^{2,4}

100% (56/56) of adult patients in the 26-week Study 311 demonstrated complete C5 inhibition after the first infusion^{2,4*}

COMPLETE TMA response was achieved in the majority of adult patients taking ULTOMIRIS in Study 311²



- **100% (30/30)** of complete TMA responses were maintained through all available follow-up in adult patients^{2‡}
- **>99.5%** of all free C5 serum samples in adult patients showed complete inhibition of C5 throughout the 6-month study period with ULTOMIRIS^{4*}

SUSTAINED: ULTOMIRIS demonstrated **8 weeks** of sustained C5 inhibition in Study 311, creating opportunity to discontinue dialysis in adult patients²

At 26 weeks

An opportunity for your adult patients to discontinue dialysis

- 17 of the 29 patients (59%) who required dialysis at study entry discontinued dialysis by the end of available follow-up^{2†}
- 21 of 27 patients (78%) who were off dialysis were still not on dialysis at last available follow-up^{2†}

Potential for recovery of kidney function in your adult patients

- Mean eGFR was 51.8 mL/min/1.73 m² at end of study, a 35.9 mL/min/1.73 m² (227%) mean increase from baseline^{2†}
- Normalization of mean platelet count (an individual component of complete TMA response) occurred by Day 8 of treatment with ULTOMIRIS. In contrast, improvements in renal function occurred more gradually over the 26-week treatment evaluation period, and in some patients continued in the 52-week extension period^{6,8}

Study 311 assessed efficacy and safety of ULTOMIRIS in adult patients^{2,4,8}

- 26-week, open-label, single-arm study of adult patients (N=56)²
- Inclusion: platelet count $\leq 150 \times 10^9/L$, evidence of hemolysis such as an elevation in serum LDH, and serum creatinine above the upper limits of normal or required dialysis²
- Exclusion: patients with TMA due to ADAMTS13 deficiency, STEC-HUS, and genetic defect in cobalamin C metabolism²
- 8 patients were immediately postpartum, 48 had received pretreatment PE/PI, and 27 had been in the ICU⁴
- Primary endpoint: complete TMA response,[†] which comprised: platelet count normalization ($\geq 150 \times 10^9/L$), serum LDH normalization ($\leq 246 U/L$), and $\geq 25\%$ improvement in serum creatinine from baseline^{2,4}
- Select secondary endpoints: time to complete TMA response and complete TMA response status over time, dialysis requirement and CKD stage as evaluated by eGFR, hemoglobin response, and change from baseline in quality of life⁸

*As measured by free C5 serum concentration of <0.5 mcg/mL.²

[†]Complete TMA response was defined as normalization of hematological parameters (platelet count and LDH) and $\geq 25\%$ improvement in serum creatinine from baseline during the 26-week initial evaluation period. Patients had to meet all criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart and any measurement in between.²

[‡]Secondary endpoint.⁸

ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ICU = intensive care unit; PE/PI = plasma exchange/plasma infusion; STEC-HUS = Shiga toxin *E. coli*-related hemolytic uremic syndrome; TMA = thrombotic microangiopathy.

STUDY 311: SAFETY PROFILE OF ULTOMIRIS IN ADULT PATIENTS WITH ATYPICAL-HUS

Adverse Reactions Reported in $\geq 10\%$ of ULTOMIRIS-Treated Adult Patients With Atypical-HUS²

Body System Adverse Reaction	Adult Patients (N=58)	
	All Grades [‡] (n=53) n (%)	\geq Grade 3 (n=14) n (%)
Blood and lymphatic system disorders		
Anemia	8 (14)	0 (0)
Gastrointestinal disorders		
Diarrhea	18 (31)	2 (3)
Nausea	15 (26)	2 (3)
Vomiting	15 (26)	2 (3)
Constipation	8 (14)	1 (2)
Abdominal pain	7 (12)	1 (2)
General disorders and administration site conditions		
Pyrexia	11 (19)	1 (2)
Edema peripheral	10 (17)	0 (0)
Fatigue	8 (14)	0 (0)
Infections and infestations		
Upper respiratory tract infection*	15 (26)	0 (0)
Urinary tract infection	10 (17)	5 (9)
Gastrointestinal infection [†]	8 (14)	2 (3)
Metabolism and nutrition disorders		
Hypokalemia	6 (10)	1 (2)
Musculoskeletal and connective tissue disorders		
Arthralgia	13 (22)	0 (0)
Back pain	7 (12)	1 (2)
Muscle spasms	6 (10)	0 (0)
Pain in extremity	6 (10)	0 (0)
Nervous system disorders		
Headache	23 (40)	1 (2)
Psychiatric disorders		
Anxiety	8 (14)	1 (2)
Respiratory, thoracic, and mediastinal disorders		
Cough	10 (17)	0 (0)
Dyspnea	10 (17)	1 (2)
Skin and subcutaneous tissue disorders		
Alopecia	6 (10)	0 (0)
Dry skin	6 (10)	0 (0)
Vascular disorders		
Hypertension	14 (24)	7 (12)

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The most frequent adverse reactions reported in $\geq 20\%$ of adult patients treated with ULTOMIRIS were²:

- diarrhea
- upper respiratory tract infection
- headache
- nausea
- arthralgia
- hypertension
- vomiting

Clinically relevant adverse reactions include viral tonsillitis (in $< 10\%$ of patients) and infusion-related reactions (in 3% of patients).²

Serious adverse reactions were reported in 42 (57%) adult and pediatric patients with atypical-HUS receiving ULTOMIRIS. The most frequent serious adverse reactions reported in more than 2 patients (2.7%) treated with ULTOMIRIS were²:

- hypertension
- pneumonia
- abdominal pain

Four patients died during the adult atypical-HUS study. Patient deaths were determined by study investigators as unrelated to study drug; the cause of death was sepsis in two patients and intracranial hemorrhage in one patient. The fourth patient, who was excluded from the trial after a diagnosis of STEC-HUS, died due to pretreatment cerebral arterial thrombosis.^{2,8}

*Grouped term includes nasopharyngitis, pharyngitis, upper respiratory tract infection, rhinitis, viral upper respiratory tract infection, rhinovirus infection, viral pharyngitis, rhinorrhea, and oropharyngeal pain.

[†]Grouped term includes gastroenteritis, gastrointestinal infection, enterocolitis infection, infectious colitis, and enterocolitis.

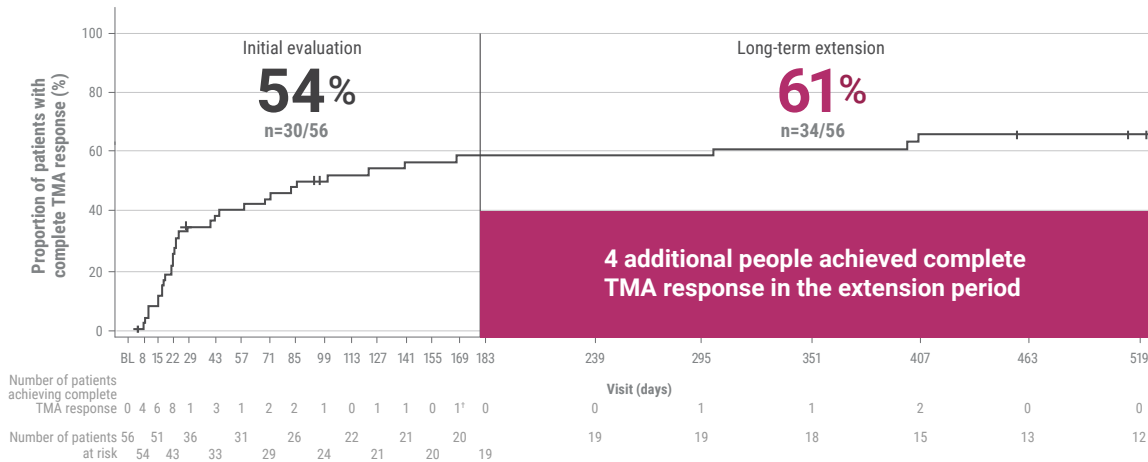
[‡]Graded per CTCAE v5.0.

CTCAE=Common Terminology Criteria for Adverse Events.

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52-WEEK EXTENSION OF STUDY 311 FOR ULTOMIRIS IN ADULT PATIENTS WITH ATYPICAL-HUS

COMPLETE TMA response was achieved in the majority of adult patients taking ULTOMIRIS^{6*}



SUSTAINED at 52 weeks: an opportunity for your adult patients to discontinue dialysis⁶

- 100% of patients who discontinued dialysis (17/17) stayed off dialysis

The extension period aimed to assess the safety and efficacy of ULTOMIRIS over a longer period of time for adults who completed the initial evaluation period^{2,6,8}

A total of 56 adult patients with atypical-HUS who were naive to complement inhibitor treatment prior to study entry were evaluated for efficacy. Of these, 49 patients completed the 26-week initial evaluation period. These patients entered the extension period of up to 4.5 years, with an interim analysis at 52 weeks. See complete study design at UltomirisHCP.com/aHUS.

Safety outcomes at the last available follow-up with ULTOMIRIS (n=58)⁶

Event Type	Day 1-183		Day 1 until last available follow-up	
	n (%)	Events	n (%)	Events
Any AE	58 (100.0)	696	58 (100.0)	986
Treatment related	19 (32.8)	50	20 (34.5)	66
Not treatment related	58 (100.0)	646	58 (100.0)	920
Any SAE	28 (48.3)	60	33 (56.9)	84
Fatal TEAEs	3 (5.2)	3	3 (5.2)	3
Study discontinuation owing to				
TEAEs	3 (5.2)	3	3 (5.2)	3
TESAEs	3 (5.2)	3	3 (5.2)	3
Drug discontinuation owing to				
TEAEs	3 (5.2)	3	3 (5.2)	3
TESAEs	3 (5.2)	3	3 (5.2)	3
SAEs during study drug infusion	0 (0)	0	0 (0)	0
Meningococcal infections	0 (0)	0	0 (0)	0

At the last available follow-up, all patients experienced one or more AEs; 20 patients (34.5%) experienced treatment-related AEs, most often headache, diarrhea, and vomiting.⁴

A total of 33 patients (56.9%) experienced serious AEs, most often hypertension and pneumonia (5.2% each).⁶

*Complete TMA response was defined as normalization of hematological parameters (platelet count and LDH) and $\geq 25\%$ improvement in serum creatinine from baseline during the 26-week initial evaluation period. Patients had to meet all criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart and any measurement in between.² Patients who did not have a response were censored at the date of last visit when the analysis was performed.^{4,8}

[†]The patient achieved initial complete TMA response measurement at Day 169; however, confirmatory measurement was not achieved until the extension period (Day 239).⁶

AE=adverse event; HUS=hemolytic uremic syndrome; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TESAE=treatment-emergent serious adverse event.



ASSESS RISK FACTORS TO INDIVIDUALIZE TREATMENT DURATION

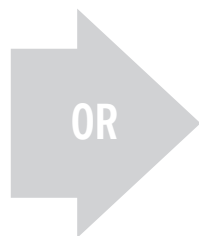
Minimum
6
months

ULTOMIRIS treatment of atypical-HUS should be a minimum duration of 6 months, after which time the treatment duration should be individualized^{2,*}

A longer treatment duration may be considered with these factors:

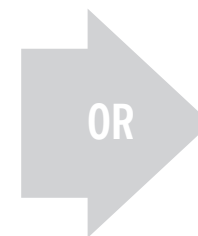
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Patient has not achieved complete TMA response after a minimum 6-month treatment with complement inhibitor^{2,9}



2

Having high risk factors for TMA recurrence (eg, genetic mutations, clinical history of TMA, family history, transplant, pediatric onset, complement biomarkers/levels, exposure to triggers)¹⁰⁻¹⁷



3

Exhibiting clinical/individual needs for maintaining therapy/disease management^{2,6,9}

Minimum
12
months

After ULTOMIRIS discontinuation, continue following up with your patient and monitor for clinical symptoms and laboratory signs of TMA complications for at least 12 months^{2†}

With untreated atypical-HUS, the risk of TMA complications may be lifelong¹⁴

TMA complications post-discontinuation can be identified if any of the following is observed²:

- Clinical symptoms of TMA, including changes in mental status, seizures, angina, dyspnea, thrombosis, or increasing blood pressure
- In addition, at least 2 of the following laboratory signs observed concurrently with results confirmed by a second measurement 28 days apart with no interruption:
 - A decrease in platelet count of 25% or more as compared to either baseline or to peak platelet count during ULTOMIRIS treatment
 - An increase in serum creatinine of 25% or more as compared to baseline or to nadir during ULTOMIRIS treatment
 - An increase in serum LDH of 25% or more as compared to baseline or to nadir during ULTOMIRIS treatment

Of the patients who have had a TMA manifestation and have discontinued C5 inhibition therapy, approximately **25% to 30% will experience relapse**^{11,15}

There are no specific data on ULTOMIRIS discontinuation²

If TMA complications occur after ULTOMIRIS discontinuation, consider reinitiating ULTOMIRIS treatment or initiating appropriate organ-specific supportive measures²

*Due to the heterogeneous nature of atypical-HUS events and patient-specific risk factors.²

†Assess discontinuation of ULTOMIRIS based on clinical judgment, including TMA relapse risk and complete TMA response. There are no specific data on ULTOMIRIS discontinuation.²

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STUDY 312: ULTOMIRIS IN PEDIATRIC PATIENTS WITH ATYPICAL-HUS

IMMEDIATE C5 inhibition was observed on Day 1 in pediatric patients in the **26-week Study 312**^{2,5*}

100% (14/14) of pediatric patients in the 26-week Study 312 demonstrated complete C5 inhibition after the first infusion^{2,5}

COMPLETE TMA response was achieved in 10 out of 14 pediatric patients taking ULTOMIRIS in Study 312^{2†}

Components of Complete TMA Response Observed in Study 312²

93%

(95% CI: 66%-99%)
n=13

Platelet Count
Normalization

86%

(95% CI: 57%-98%)
n=12

LDH Normalization

79%

(95% CI: 49%-95%)
n=11

≥25% Improvement in Serum
Creatinine From Baseline

Hematologic Normalization²

86%

(95% CI: 57%-98%)
n=12

Platelet Count
& LDH Normalization

Complete TMA Response²

71%
(95% CI: 42%-92%)
n=10

- **100% (10/10)** of complete TMA responses were maintained through all available follow-up in pediatric patients^{2‡}
- Free C5 serum samples in pediatric patients showed immediate, complete inhibition of C5 sustained throughout the 26-week period^{2,5*}

SUSTAINED: ULTOMIRIS demonstrated **4 or 8 weeks** (depending on body weight) of sustained C5 inhibition in Study 312, creating opportunity to discontinue dialysis in pediatric patients²

At 26 weeks

An opportunity for your pediatric patients to discontinue dialysis

- 4 of the 5 patients (80%) who required dialysis at study entry discontinued dialysis after the first month in study and for the duration of ULTOMIRIS treatment^{2‡}
- No patient started dialysis during the study^{2‡}

Potential for recovery of kidney function in your pediatric patients

- Mean eGFR was 108.0 mL/min/1.73 m² at end of study, a 79.6 mL/min/1.73 m² (280%) mean increase from baseline^{2‡}

Study 312 assessed efficacy and safety of ULTOMIRIS in pediatric patients^{2,18}

- 26-week, multicenter, open-label, single-arm study of eculizumab-naïve patients (N=14) with documented diagnosis of atypical-HUS²
- Inclusion: platelet count $\leq 150 \times 10^9/L$, evidence of hemolysis such as an elevation in serum LDH, and serum creatinine $\geq 97.5\%$ percentile at screening or required dialysis²
- Exclusion: patients with TMA due to ADAMTS13 deficiency, STEC-HUS, and genetic defect in cobalamin C metabolism²
- Primary endpoint: complete TMA response,[‡] which comprised: platelet count normalization ($\geq 150 \times 10^9/L$), serum LDH normalization (less than upper limit of normal), and $\geq 25\%$ improvement in serum creatinine from baseline²
- Select secondary endpoints: time to complete TMA response and complete TMA response status over time, dialysis requirement, and CKD stage as evaluated by eGFR, hemoglobin response, and change from baseline in quality of life¹⁸

Data reported here are the interim analysis results of Study 312 in the cohort of eculizumab inhibitor-naïve patients, included in the US ULTOMIRIS Prescribing Information.²

*As measured by free C5 serum concentration of <0.5 mcg/mL.²

†Complete TMA response was defined as normalization of hematological parameters (platelet count and LDH) and $\geq 25\%$ improvement in serum creatinine from baseline during the 26-week initial evaluation period. Patients had to meet all criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between.²

‡Secondary endpoint.¹⁸

ADAMTS13=a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; LDH=lactate dehydrogenase; STEC-HUS=Shiga toxin *E. coli*-related hemolytic uremic syndrome; TMA=thrombotic microangiopathy.

STUDY 312: SAFETY PROFILE OF ULTOMIRIS IN PEDIATRIC PATIENTS WITH ATYPICAL-HUS

Adverse Reactions Reported in $\geq 10\%$ of ULTOMIRIS-Treated Pediatric Patients With Atypical-HUS²

Body System Adverse Reaction	Pediatric Patients (N=16)	
	All Grades [†] (n=16) n (%)	\geq Grade 3 (n=6) n (%)
Blood and lymphatic system disorders		
Anemia	2 (13)	1 (6)
Lymphadenopathy	2 (13)	0 (0)
Gastrointestinal disorders		
Diarrhea	6 (38)	0 (0)
Constipation	4 (25)	0 (0)
Vomiting	4 (25)	1 (6)
Abdominal pain	3 (19)	0 (0)
Nausea	2 (13)	0 (0)
General disorders and administration site conditions		
Pyrexia	8 (50)	0 (0)
Infections and infestations		
Upper respiratory tract infection*	7 (44)	1 (6)
Gastroenteritis viral	2 (13)	2 (13)
Pneumonia	2 (13)	1 (6)
Tonsillitis	2 (13)	0 (0)
Injury, poisoning, and procedural complications		
Contusion	3 (19)	0 (0)
Investigations		
Vitamin D decreased	3 (19)	0 (0)
Metabolism and nutrition disorders		
Decreased appetite	2 (13)	0 (0)
Iron deficiency	2 (13)	0 (0)
Musculoskeletal and connective tissue disorders		
Myalgia	3 (19)	0 (0)
Pain in extremity	2 (13)	0 (0)
Nervous system disorders		
Headache	5 (31)	0 (0)
Respiratory, thoracic, and mediastinal disorders		
Cough	3 (19)	0 (0)
Dyspnea	2 (13)	0 (0)
Skin and subcutaneous tissue disorders		
Rash	3 (19)	0 (0)
Vascular disorders		
Hypertension	4 (25)	1 (6)
Hypotension	2 (13)	0 (0)

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



The most frequent adverse reactions reported in $\geq 20\%$ of pediatric patients treated with ULTOMIRIS were²:

- diarrhea
- constipation
- vomiting
- pyrexia
- upper respiratory tract infection
- headache
- hypertension

Clinically relevant adverse reactions in $< 10\%$ of patients included viral infection.²

Serious adverse reactions were reported in 42 (57%) adult and pediatric patients with atypical-HUS receiving ULTOMIRIS. The most frequent serious adverse reactions reported in more than 2 patients (2.7%) treated with ULTOMIRIS were²:

- hypertension
- pneumonia
- abdominal pain

*Grouped term includes nasopharyngitis, pharyngitis, upper respiratory tract infection, rhinitis, viral upper respiratory tract infection, rhinovirus infection, viral pharyngitis, rhinorrhea, and oropharyngeal pain.

[†]Graded per CTCAE v5.0.

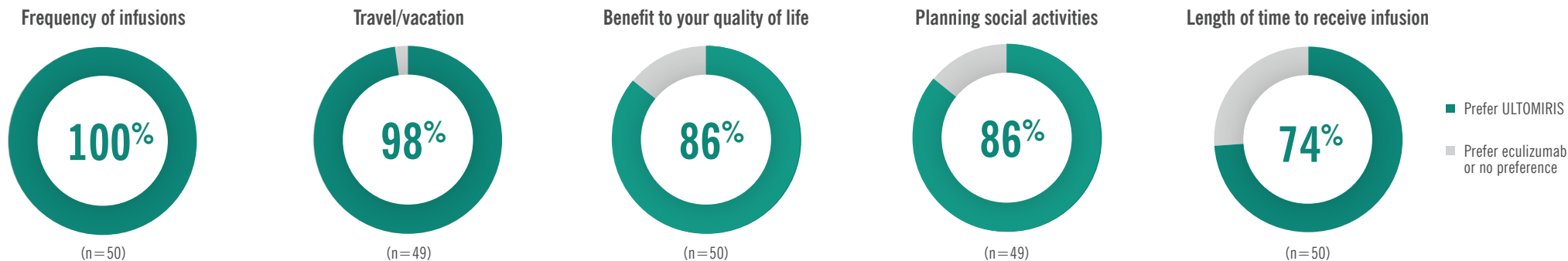
CTCAE=Common Terminology Criteria for Adverse Events.

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

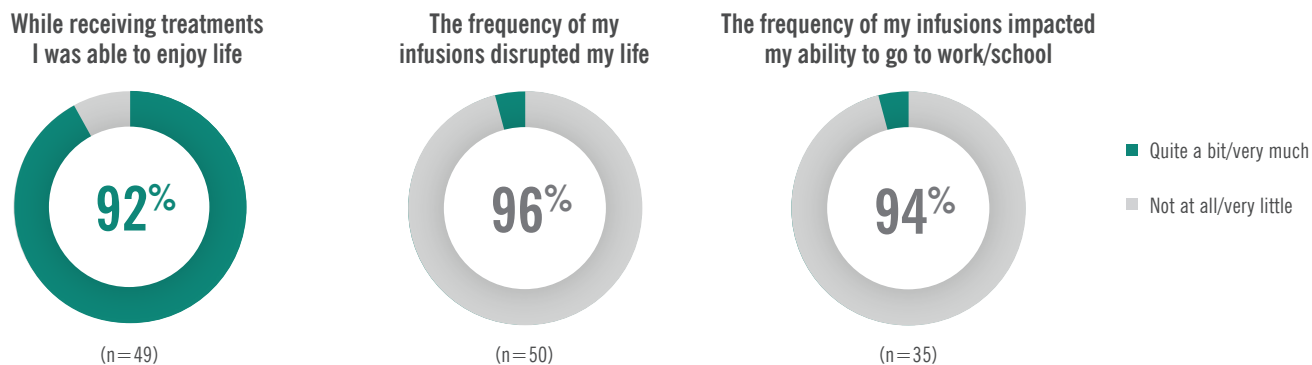
PATIENTS PREFERRED ULTOMIRIS

In a survey of adult US patients (N=50) with confirmed atypical-HUS who had previously received eculizumab and ≥ 3 doses of ULTOMIRIS^{19*}

Patient-reported survey: proportion of patients (%) who preferred ULTOMIRIS regarding specific parameters¹⁹



ULTOMIRIS impacted patients: Adult patients were asked how ULTOMIRIS impacted the following domains, based on their experience during their treatment with SOLIRIS and after switching to ULTOMIRIS¹⁹



• For the same questions, results seen with eculizumab were 66% (n=50), 28% (n=50), and 40% (n=35), respectively

Patients treated with ULTOMIRIS require fewer maintenance infusions than those treated with eculizumab (for patients weighing >20 kg), at 7 vs 26 infusions per year^{2,21}

For patients who responded "not applicable," responses were excluded from the percentage calculation for each question. Mean durations of eculizumab and ULTOMIRIS treatment were 46.9 and 12.9 months, respectively.¹⁹

*A web-based survey of US adults (N=50) with confirmed diagnosis of atypical-HUS who had previously received eculizumab and ≥ 3 doses of ravulizumab.¹⁹

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



ALEXION: A LONG-STANDING HISTORY OF COMMITMENT TO SUPPORTING PATIENTS WITH RARE DISEASES



Personalized Patient Support from Alexion

1.888.765.4747 • OneSource@Alexion.com
AlexionOneSource.com/Ultomiris

\$0 out-of-pocket costs for eligible patients*†



Get started here, with the **OneSource enrollment form**

bit.ly/3LDZPYG

Our ongoing commitment includes 20 years of complement research experience and more than a decade delivering complement inhibition in the clinical setting. Plus, we created OneSource™ to support you and your patients every step of the way.

- OneSource is a complimentary, personalized patient support program that connects patients, families, and caregivers facing complement-mediated diseases with a dedicated team of support professionals and advocates

Copay assistance

- OneSource will provide financial assistance by covering eligible patients' out-of-pocket medication and infusion costs associated with ULTOMIRIS
- Valid only for patients with commercial insurance who have a valid prescription for a US FDA-approved indication of ULTOMIRIS. Not valid for costs eligible to be reimbursed by government insurance programs‡ or other federal or state programs (including any state prescription drug assistance programs)
- Additional requirements may apply. Contact Alexion OneSource at [1.888.765.4747](tel:18887654747) or OneSource@Alexion.com for more information on patient eligibility

OneSource representatives also assist with



Education



Ongoing Support



Health Insurance Navigation



Community Connections



ALEXION ACCESS NAVIGATOR

Alexion Access Navigator is a dedicated resource where US healthcare professionals and their offices can find downloadable access and reimbursement materials, including indication-specific coding and billing guides, sample letters of medical necessity, and a link to the REMS program.

AlexionAccessNavigator.com/Ultomiris

*Based on typical commercial patient out-of-pocket deductible limits.

†Additional terms and conditions apply. Please contact OneSource with additional questions.

‡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.

REMS=Risk Evaluation and Mitigation Strategies.

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

#1 PRESCRIBED
TREATMENT
for
atypical-HUS^{1,2*}

Consider a treatment used for more than
1,000 patients with atypical-HUS,^{1†} and more
than 9,000 patient-years across all
ULTOMIRIS indications^{3‡}

Immediate, complete, and sustained[§] C5 inhibition with
ULTOMIRIS in adult and pediatric patients with atypical-HUS^{2,4,5}

IMMEDIATE

100% (n=70) of adult and pediatric patients

had complete C5 inhibition at the end of the first infusion of ULTOMIRIS.^{2,4-6}

COMPLETE

54% (n=30/56; 95% CI: 40%-67%) of adult and 71% (n=10/14; 95% CI: 42%-92%) of pediatric patients

met the composite endpoint of complete TMA response with ULTOMIRIS by 26 weeks.^{2||¶} Four additional adult patients who did not achieve a complete TMA response at 26 weeks did so with continued ULTOMIRIS treatment at 52 weeks.^{2,6}

SUSTAINED

Up to 8 weeks of sustained C5 inhibition and the possibility to live dialysis-free in
adult and pediatric patients.^{2#}



For more information on support resources for atypical-HUS,
please visit UltomirisHCP.com/aHUS

*ULTOMIRIS had more than a 50% share of patients with atypical-HUS actively taking Alexion medications every month from August 2021 through August 2023.¹

[†]Reflects the number of patients with atypical-HUS currently on ULTOMIRIS as of August 2023.¹

[‡]Based on a cumulative search of the Alexion safety database for real-world ravulizumab data from December 2018 to December 2022 across all indications.³ See all indications at UltomirisHCP.com.

[§]In the majority (93%) of adult and pediatric patients with atypical-HUS throughout the entire 26-week treatment period.²

^{||}Complete TMA response was defined as normalization of hematological parameters (platelet count and LDH) and $\geq 25\%$ improvement in serum creatinine from baseline during the 26-week initial evaluation period. Patients had to meet all criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart and any measurement in between.²

[¶]Interim results of a 26-week, multicenter, open-label, single-arm study of 14 SOLIRIS-naïve patients with documented diagnosis of atypical-HUS.²

[#]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).²

References: 1. Data on file. Atypical-HUS market access dashboard. Alexion Pharmaceuticals, Inc.; 2023. 2. ULTOMIRIS. Prescribing information. Alexion Pharmaceuticals, Inc. 3. Fam S, et al. Poster presented at: The 9th Congress of the European Academy of Neurology (EAN); July 1-4, 2023; Budapest, Hungary. 4. Rondeau E, et al. *Kidney Int.* 2020;97(6):1287-1296. 5. Ariceta G, et al. *Kidney Int.* 2021;100:225-237. 6. Barbour T, et al. *Kidney Int Rep.* (article and supplement) 2021;6(6):1603-1613. 7. Sheridan D, et al. *PLoS One.* 2018;13(4):e0195909. 8. Data on file [ALXN1210-aHUS-311CSR]. 9. Laurence J. *Clin Adv Hematol Oncol.* 2020;18(4):221-230. 10. Noris M, Mescafa F, Remuzzi G. *Nat Rev Nephrol.* 2012;8:622-633. 11. Menne J, et al. *BMC Nephrol.* 2019;20(1):125. 12. Ariceta G, et al. *Clin Kidney J.* 2021;14(9):2075-2084. 13. Duineveld C, et al. *Kidney Int Rep.* 2023;8(4):715-726. 14. Asif A, Nayer A, Haas CS. *J Nephrol.* 2017;30(3):347-362. 15. Macia M, et al. *Clin Kidney J.* 2017;10(3):310-319. 16. Timmermans SAMEG, et al. *J Am Soc Nephrol.* 2018;29(8):2234-2243. 17. Fakhouri F, et al. *J Am Soc Nephrol.* 2010;21(5):859-867. 18. Data on file [ALXN1210-aHUS-312CSR]. 19. Mauch T, et al. *J Comp Eff Res.* 2023;12(9):e230036. 20. Data on file. aHUS ULTOMIRIS Calculator. Alexion Pharmaceuticals, Inc.; 2023. 21. SOLIRIS. Prescribing information. Alexion Pharmaceuticals, Inc.

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US/ULT-a/0130 V5 06/2024

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

SELECT IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

ULTOMIRIS, a complement inhibitor, increases the risk of serious infections caused by *Neisseria meningitidis* [see *Warnings and Precautions* (5.1)] Life-threatening and fatal meningococcal infections have occurred in patients treated with complement inhibitors. These infections may become rapidly life-threatening or fatal if not recognized and treated early.

- Complete or update vaccination for meningococcal bacteria (for serogroups A, C, W, Y, and B) at least 2 weeks prior to the first dose of ULTOMIRIS, unless the risks of delaying ULTOMIRIS therapy outweigh the risk of developing a serious infection. Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against meningococcal bacteria in patients receiving a complement inhibitor. See *Warnings and Precautions* (5.1) for additional guidance on the management of the risk of serious infections caused by meningococcal bacteria.
- Patients receiving ULTOMIRIS are at increased risk for invasive disease caused by *Neisseria meningitidis*, even if they develop antibodies following vaccination. Monitor patients for early signs and symptoms of serious meningococcal infections and evaluate immediately if infection is suspected.

Because of the risk of serious meningococcal infections, ULTOMIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called ULTOMIRIS and SOLIRIS REMS [see *Warnings and Precautions* (5.2)].



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

ALEXION[®]
AstraZeneca Rare Disease