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

TRANSITION TO ULTOMIRIS IN A PATIENT WITH ATYPICAL HEMOLYTIC UREMIC SYNDROME (ATYPICAL-HUS): A CASE STUDY


Actor portrayal

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).

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.

This is Andrew.* He is 48 years old and has atypical-HUS.

Atypical-HUS Case Study: Transition to ULTOMIRIS

"LIFE IS UNPREDICTABLE, ESPECIALLY WITH A RARE DISEASE. THROUGH THE ROLLER COASTER, I'VE LEARNED A LOT ABOUT MYSELF AND MY CAPABILITIES."


Actor portrayal

*NAME HAS BEEN CHANGED TO PROTECT PRIVACY.

Case presented by:

Edward R. George, MD

Dr George is a paid consultant of Alexion® Pharmaceuticals, Inc., and was compensated for his time.

Based on an actual patient

Andrew

Age: 48 years old[a]

Height: 183 cm (6 ft)

Weight: 95.5 kg (211 lbs)

Diagnosed with atypical-HUS

Family History

- Maternal uncle died in early thirties (unexplained)

A long journey to a diagnosis of atypical-HUS

Select signs and symptoms

- At age 25, Andrew went to the ER and was diagnosed with acute end stage renal disease
  - Presented with headache, hypertension (BP 160/100), and foamy dark urine
  - Put on dialysis
- A few months after getting his diagnosis, he received his first kidney transplant from his stepmother
  - Unfortunately, due to immunologic acute humoral rejection of the transplant, transplant was removed approximately 1 year later and he was put on dialysis
- During this time, Andrew dealt with guilt and depression
- He also had 3 AVFs, all of which thrombosed
- At age 34, Andrew received his second kidney transplant
  - Showed evidence of:
    - Graft-related pain, renal failure, and edema
    - TMA (by renal biopsy)
    - Low hemoglobin, increased LDH, low platelet counts, and schistocytes in peripheral blood smear
- Diagnosed with TTP and underwent plasmapheresis treatment
  - Andrew continued to worsen; second kidney transplant was removed and he was put on dialysis
- Because of the TTP diagnosis, Andrew was ineligible for a third kidney transplant

LAB VALUES AT SECOND TRANSPLANT REJECTION	
Hemoglobin (g/L) (reference range: 14-18 g/dL)[1]	8.2
LDH (U/L) (reference range: 100-200 U/L)[1]	929
Platelet count (cells/mm^3) (reference range: 150,000-350,000 cells/mm^3)[1]	86,000
Creatinine (mg/dL) (reference range: 0.6-1.2 mg/dL)[1]	3.35
BUN (reference range: 8-23 mg/dL)[1]	50

AVF=arteriovenous fistula; BP=blood pressure; BUN=blood urea nitrogen; HUS=hemolytic uremic syndrome; LDH=lactate dehydrogenase; TMA=thrombotic microangiopathy; TTP=thrombotic thrombocytopenic purpura.

[a]Andrew's age as of 2021.

SELECT IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

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"WHEN I REALIZED MY DIAGNOSIS MIGHT NOT BE CORRECT, I CALLED MY NEPHROLOGIST. SHE SENT ME TO A HEMATOLOGIST AND HE CONDUCTED A NUMBER OF TESTS. AND FINALLY, AFTER MORE THAN 15 YEARS, I KNEW THE CAUSE OF MY ILLNESS: I HAD ATYPICAL-HUS."

— Andrew

A second opinion leading to a new diagnosis

- At this time, Andrew sought to learn all he could about TTP and found another patient with a similar medical history as himself, but who had been diagnosed with atypical-HUS, not TTP
- Andrew reached out to his nephrologist and was referred to see Dr George, a hematologist and a key partner in Andrew's healthcare journey for several years to come. Dr George was able to provide a second opinion for Andrew's diagnosis of atypical-HUS

Diagnosing atypical-HUS requires excluding other conditions[2-4]

- Dr George ran blood tests that showed ADAMTS13 activity of 100%, which ruled out TTP diagnosis[2,3,a]
- Additionally, Andrew had a negative stool test for Shiga toxin-producing *E coli* and a negative Coombs test. The negative Shiga toxin panel ruled out STEC-HUS, another disorder that can commonly cause TMA[2,3]
- Family and medical history were also reviewed. Lab values were reassessed, including:
  - Low platelet count and high LDH levels
  - TMA on renal biopsy
  - Multiple thrombosed AVFs
  - Failing plasmapheresis treatment
  - Schistocytes on blood smear
- Together this indicated that Andrew had atypical-HUS: a rare, life-threatening disease caused by dysregulation of the alternative pathway of the complement system[2,3]
- With a more complete understanding of his condition, new disease management and treatment possibilities emerged for Andrew
  - He was told that he was now eligible for a third kidney transplant
- Andrew received his third kidney transplant at the age of 39

[a]>5% ADAMTS13 activity=atypical-HUS. ≤5% ADAMTS13 activity=TTP (range found in published data is 5%-10%).
ADAMTS13=a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; AVF=arteriovenous fistula; STEC=Shiga toxin-producing *Escherichia coli*.

"BASED ON THE CLINICAL DATA PROVIDED BY MY DOCTOR, WE FELT LIKE ULTOMIRIS WOULD BE GREAT FOR ME."

Treatment discussion

- Andrew was receiving SOLIRIS® (eculizumab) when he learned about ULTOMIRIS, the first and only long-acting C5 inhibitor administered every 4 or 8 weeks (depending on body weight) in adults and children 1 month of age and older with atypical-HUS. Not indicated for STEC-HUS[5,6]
  - For patients switching from SOLIRIS to ULTOMIRIS, administer the loading dose of ULTOMIRIS at the time of the next scheduled SOLIRIS dose, and then administer maintenance doses once every 8 weeks or every 4 weeks (depending on body weight), starting 2 weeks after loading dose administration[6]
- After looking through the clinical data for ULTOMIRIS, the FDA-approved prescription therapy for adults and children 1 month of age and older with atypical-HUS, Andrew was transitioned to ULTOMIRIS[6]

What is ULTOMIRIS?

- ULTOMIRIS, built on the foundation of eculizumab, is a C5 inhibitor that has an ~4X longer half-life and a dosing schedule of every 8 weeks for adult patients, starting 2 weeks after an initial loading dose[5-7,a,b]

Adult study design

- The adult study was a 26-week, open-label, single-arm study of 56 adult patients who displayed signs of TMA and were naïve to complement inhibitor treatment[6]
- Primary endpoint: complete TMA response, defined as normalization of hematological parameters (platelet count and LDH normalization)[c] and ≥25% improvement in serum creatinine from baseline. Patients had to meet all criteria for the primary endpoint of a complete TMA response at 2 separate assessments obtained at least 4 weeks (28 days) apart and any measurement in between[6]
- Select secondary endpoints in the adult study included: 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 life[6,8]

Adult study results

- Complete TMA response was observed in 30 of the 56 patients (54%) during the 26-week initial evaluation period. One additional patient had a complete TMA response that was confirmed after the 26-week initial evaluation period. Complete TMA response was achieved at a median time of 86 days (range: 6 to 169 days). The median duration of complete TMA response was 7.97 months (range: 2.52 to 16.69 months). All responses were maintained through all available follow-up[6]
- An increase in mean platelet count was observed after commencement of ULTOMIRIS, increasing from 118.52 x 10^9/L at baseline to 240.34 x 10^9/L at Day 8 and remaining above 227 x 10^9/L at all subsequent visits in the initial evaluation period (26 weeks)[6]
- Renal function, as measured by eGFR, was improved or maintained during ULTOMIRIS therapy. The mean eGFR (+/- SD) increased from 15.86 (14.82) at baseline to 51.83 (39.16) by 26 weeks. In patients with complete TMA response, renal function continued to improve after the complete TMA response was achieved[6]
- The most frequent adverse reactions reported in ≥20% of adult patients treated with ULTOMIRIS were upper respiratory tract infection, diarrhea, nausea, vomiting, headache, hypertension, and arthralgia. Clinically relevant adverse reactions in <10% of patients included viral tonsillitis[6]

Efficacy results in atypical-HUS during the 26-week initial evaluation period (ALXN1210-aHUS-311)

	TOTAL	RESPONDER	
		n	PROPORTION (95% CI)[d]
Complete TMA response	**56**	**30**	**54%** (40%-67%)
Components of complete TMA response			
Platelet count normalization	**56**	**47**	**84%** (72%-92%)
LDH normalization	**56**	**43**	**77%** (64%-87%)
≥25% improvement in serum creatinine from baseline	**56**	**33**	**59%** (45%-72%)
Hematologic normalization (platelet count and LDH normalization)	**56**	**41**	**73%** (60%-84%)

[a]The mean (SD) terminal elimination half-life and clearance of intravenous ULTOMIRIS in patients with atypical-HUS are 51.8 (16.2) days and 0.08 (0.04) L/day, respectively. Half-life of eculizumab is 11.25 to 17.25 days.[5,6]

[b]Targeted engineering to incorporate 4 amino acid substitutions designed to reduce TMDD 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.[7]

[c]Includes ≥150 x 10^9/L for platelet count and a value less than the upper limit of normal for LDH.

[d]95% CIs for the proportion were based on exact confidence limits using the Clopper-Pearson method.

CI=confidence interval; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; FcRn=neonatal Fc receptor; LDH=lactate dehydrogenase; TMA=thrombotic microangiopathy; TMDD=target-mediated drug disposition.

SELECT IMPORTANT SAFETY INFORMATION

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.

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.

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"OVERALL, MY TRANSITION TO ULTOMIRIS WENT WELL. I RECEIVED THE STARTING DOSE OF ULTOMIRIS AT THE TIME OF MY NEXT SCHEDULED DOSE OF SOLIRIS, AND SO FAR, ULTOMIRIS IS WORKING WELL FOR ME."

— Andrew

ULTOMIRIS treatment

- Andrew was placed on an initial loading dose of ULTOMIRIS, using weight-based dosing, at the time of his next scheduled SOLIRIS dose[6]
  - Andrew received a vaccination for *Neisseria meningitidis,* according to Advisory Committee on Immunization Practices (ACIP) guidelines, to reduce the risk of serious infection more than two weeks before starting ULTOMIRIS[6]
- Andrew was given a maintenance dose of ULTOMIRIS every 8 weeks, starting 2 weeks after the initial loading dose[6]
- Following the transition to ULTOMIRIS, LDH levels and renal function have remained stable[a]
- Andrew has been happy with his choice to transition to ULTOMIRIS
- Andrew experienced a mild headache for a week after first infusion
  - The most frequent adverse reactions reported in ≥20% of adult and pediatric patients treated with ULTOMIRIS were upper respiratory tract infection, diarrhea, nausea, vomiting, headache, hypertension, and pyrexia[6]
- Andrew did not report any signs or symptoms of infusion-related reactions
  - Monitor the patient for at least one hour following completion of the infusion for signs or symptoms of an infusion-related reaction[6]
  - Administration of ULTOMIRIS may result in infusion-related 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. Interrupt ULTOMIRIS infusion and institute appropriate supportive measures if signs of cardiovascular instability or respiratory compromise occur[6]

LAB VALUES	DAY 1[b]	WEEK 2	WEEK 10	WEEK 18	WEEK 26
Hemoglobin (g/L) (reference range: 14-18 g/dL)[1]	10.1	9.9	10.6	10.1	10.6
LDH (U/L) (reference range: 100-200 U/L)[1]	182	190	205	180	180
Platelet count (cells/mm^3) (reference range: 150,000-350,000 cells/mm^3)[1]	146	171	169	178	186
Creatinine (mg/dL) (reference range: 0.6-1.2 mg/dL)[1]	1.64	1.51	1.5	1.6	1.5
BUN (reference range: 8-23 mg/dL)[1]	21	25	20	21	16

[a]Secondary endpoint.
[b]Day 1 is relative to first dose of ULTOMIRIS administered intravenously.

SELECT IMPORTANT SAFETY INFORMATION

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.

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.

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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.

Thromboembolic Event Management

The effect of withdrawal of anticoagulant therapy during treatment with ULTOMIRIS has not been established. Treatment should not alter anticoagulant management.

Infusion-Related Reactions

Administration of ULTOMIRIS may result in systemic infusion-related reactions, including anaphylaxis and hypersensitivity reactions. In clinical trials, infusion-related reactions occurred in approximately 1 to 7% of patients, including lower back pain, abdominal pain, muscle spasms, drop or elevation in blood pressure, rigors, limb discomfort, drug hypersensitivity (allergic reaction), and dysgeusia (bad taste). These reactions did not require discontinuation of ULTOMIRIS. If signs of cardiovascular instability or respiratory compromise occur, interrupt ULTOMIRIS and institute appropriate supportive measures.

ADVERSE REACTIONS

Most common adverse reactions in patients with aHUS (incidence ≥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 ≥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.

USE IN SPECIFIC POPULATIONS

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ULTOMIRIS during pregnancy. Healthcare providers and patients may call 1-833-793-0563 or go to www.UltomirisPregnancyStudy.com to enroll in or to obtain information about the registry.

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.

References

1. American College of Clinical Pharmacy. Accessed May 03, 2021. www.accp.com/docs/sap/Lab_Values_Table_PSAP.pdf **2.** Laurence J, et al. *Clin Adv Hematol Oncol.* 2016;14(suppl 11):2-15. **3.** Berger BE. *Clin Kidney J.* 2019;12(3):338-347. **4.** Asif A, et al. *J Nephrol.* 2017;30:347-362. **5.** SOLIRIS. Prescribing information. Alexion Pharmaceuticals, Inc. **6.** ULTOMIRIS. Prescribing information. Alexion Pharmaceuticals, Inc. **7.** Sheridan D, et al. *PLoS One.* 2018;13(4):e0195909. **8.** Data on file [ALXN1210-aHUS-311 CSR].

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.

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