Actor portrayal

#1 PRESCRIBED TREATMENT FOR ATYPICAL-HUS[1,2,a]

ULTOMIRIS for the treatment of atypical-HUS in the presence of hypertensive emergency

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)*].

[a]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]
Atypical-HUS=atypical hemolytic uremic syndrome.

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.

Recognize the critical role of hypertensive emergency (HE) as a trigger for atypical-HUS[3,4]

HE may lead to thrombotic microangiopathy (TMA) and unmask atypical-HUS[3,5-7]

HE is severe hypertension with end-organ involvement[a]

- Overactivation of the complement system was found in 59% (n=17/29) of patients with hypertensive emergency and TMA[9,a]
- Patients may present with key markers of TMA[10,11]

TMA is a medical emergency requiring immediate screening for an underlying cause[4,12]

TMA is characterized by[4,10]**:**

- Microangiopathic hemolytic anemia
- Thrombocytopenia: Low platelet count (<150 x 10⁹/L or a >25% decrease in platelet count from baseline)
- 1 or more signs and symptoms of organ damage

Atypical-HUS is associated with continuous risk of complement-mediated TMA and life-threatening consequences[4,12,13]

Atypical-HUS is a result of either or both of these factors[4,12]**:**

- A patient's genetic predisposition to complement dysregulation
- Exposure to factors or conditions that trigger complement activation such as hypertensive emergency

In patients with mHTN, could TMA and atypical-HUS be more common than you realize?

In a retrospective analysis of 199 patients with mHTN[11,b]

of the patients **presented with TMA** (n=40/199)

and of them

of the patients with TMA **had atypical-HUS** (n=24/40)

While treating patients for HE, the presence of TMA should increase suspicion of atypical-HUS[11]

Other causes of TMA in patients with hypertensive emergency included drug-related mHTN, some systemic diseases, and IgA nephropathy.[7,11]

[a]Based on a 2021 cohort study of patients with TMA with severe kidney involvement (N=65) from the Limburg Renal Registry in the Netherlands and the Cliniques Universitaires Saint-Luc in Belgium.[9]
[b]Retrospective cohort analysis of hospitalized patients diagnosed with mHTN (N=199) from 2000-2020 in 8 nephrology departments in Spain.[11]

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.

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

Early diagnosis and management for atypical-HUS in the presence of hypertensive emergency is critical[4,10,12]

Studies of patients with atypical-HUS have found that…

69% had both atypical-HUS and mHTN appear around the same time (n=49/71)[10,a]

81% with both HE and atypical-HUS required dialysis at onset (n=57/70)[14,b]

65% with atypical-HUS and mHTN who did not receive appropriate treatment required a kidney transplant (n=33/51)[10,a]

62% with atypical-HUS progressed to kidney failure (n=16/26)[11,c]

In a study of 9 patients with HE who had atypical-HUS, hematological signs of TMA were uncommon, potentially reflecting smoldering cases of TMA. These cases of TMA can present as a persistent, progressive, and gradual disease course[6,15,d]

Consider screening HE patients for TMA, and then for atypical-HUS

In patients with atypical-HUS and mHTN (n=26),[11,c]

66% of patients experienced kidney loss at 5 years

Without appropriate atypical-HUS management[14,b]

The kidney loss rates of patients with HE and atypical-HUS were

64% At 1 year

77% At 5 years

[a]Retrospective analysis of patients with mHTN and atypical-HUS (N=1097) enrolled in the Global atypical-HUS Registry and followed for ≥90 days from atypical-HUS diagnosis from 2012 to 2020.[10]
[b]Based on a French retrospective cohort analysis of patients with atypical-HUS, with or without concomitant hypertensive emergency (N=137), screened between 2000 and 2016.[14]
[c]Retrospective cohort analysis of hospitalized patients diagnosed with mHTN (N=199) from 2000-2020 in 8 nephrology departments in Spain.[11]
[d]A retrospective analysis of patients with severe hypertension with biopsy-proven renal TMA (N=9) from January 2005 onward at a medical center in the Netherlands.[6]
Atypical-HUS=atypical hemolytic uremic syndrome; IgA=Immunoglobulin A; mHTN=malignant hypertension.

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

Serious Meningococcal Infections (cont'd)

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*.

Recognize the patient with hypertensive emergency at risk for atypical-HUS and respond promptly

Studies show that characteristics of patients with atypical-HUS and hypertensive emergency may include[11,14]:

- **Usually in their mid 40s or younger[a,b]**
- **Some have genetic complement abnormalities[c]**
- **Often have renal involvement and potentially severe kidney injury[a,b]**
- **May have extrarenal manifestations—including neurological[a,b]**

Consider additional characteristics that may be present in patients with atypical-HUS and hypertensive emergency[11,12]

- Taking >2 antihypertensives to normalize blood pressure—while renal function continues to decline
- Requiring dialysis at presentation
- Having a family or medical history of TMA and/or kidney failure

Can you think of a patient with hypertensive emergency who wasn't responding to therapy the way you expected?

[a]Based on a French retrospective cohort analysis of patients with atypical-HUS, with or without concomitant hypertensive emergency (N=137), screened between 2000 and 2016.[14]
[b]Retrospective cohort analysis of hospitalized patients diagnosed with mHTN (N=199) from 2000-2020 in 8 nephrology departments in Spain.[11]
[c]In 30%-40% of atypical-HUS patients, the cause is ill-defined, and the role of additional genetic or environmental factors remains debatable.[14,16]

Differential diagnosis of TMA, including atypical-HUS

Although TMA can be associated with various triggers,[a] a delayed diagnosis of atypical-HUS—preventing timely treatment with C5 inhibition—may have devastating consequences, including end-stage kidney disease[4,17]

Thrombocytopenia
Platelet count <150 x 10^9/L or >25% decrease from baseline

AND

Microangiopathic hemolysis
Schistocytes and/or elevated LDH and/or decreased haptoglobin and/or decreased hemoglobin

Plus 1 or more of the following:

Common Symptoms

- **Neurological symptoms**
- **Kidney impairment**
- **Gastrointestinal symptoms**

Other Symptoms

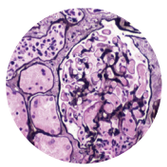
- **Cardiovascular symptoms**
- **Pulmonary symptoms**
- **Visual symptoms**

Evaluate ADAMTS13 activity and Shiga toxin/EHEC test[b]

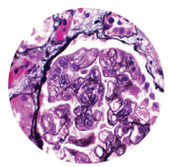
While ADAMTS13 results are awaited, a platelet count >30 x 10^9/L and/or SCr >1.7 to 2.3 mg/dL almost eliminates a diagnosis of severe ADAMTS13 deficiency (TTP)

≤5%[c] ADAMTS13 activity	**>5% ADAMTS13 activity**	**Shiga toxin/EHEC positive**
TTP	**Atypical-HUS**	**STEC-HUS**

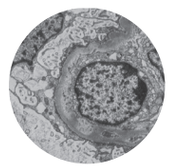
IF APPROPRIATE, A RENAL BIOPSY CAN REVEAL TMA[18,19]



Glomerular/ arteriolar thrombi



Basement membrane splitting



Basement membrane formation and early cellular interposition

Adapted from Lusco MA, et al. *Am J Kidney Dis.* 2016;68(6):e33-e34.

Although renal biopsy is not required for diagnosis of atypical-HUS, it may reveal cases of TMA[15,18]

[a]Triggers may include but are not limited to pregnancy/postpartum, hypertensive emergency, autoimmune disease, and transplant.[4]

[b]Shiga toxin/EHEC test is warranted with history/presence of GI symptoms.[4]

[c]Range found in published literature is <5%-10%.[4]

ADAMTS13=a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; atypical-HUS=atypical hemolytic uremic syndrome; C5=complement component 5; EHEC=enterohemorrhagic *Escherichia coli*; GI=gastrointestinal; LDH=lactate dehydrogenase; mHTN=malignant hypertension; SCr=serum creatinine; STEC-HUS=Shiga toxin-producing *Escherichia coli*-associated hemolytic uremic syndrome; TMA=thrombotic microangiopathy; TTP=thrombotic thrombocytopenic purpura.

ULTOMIRIS offered complete TMA response for the majority of adult patients with atypical-HUS[2,a]

Study Design

Study 311 was conducted in 56 adult patients (Full Analysis Set) with atypical-HUS who were naïve to complement inhibitor treatment prior to study entry. The study consisted of a 26-week initial evaluation period and patients could then enter a 4.5-year extension period. Long-term extension data are from an interim analysis at Week 52.[2,20,21]

Select inclusion criteria: Platelet count ≤150 x 10^9 cells/L and evidence of hemolysis (eg, elevated serum LDH, serum creatinine >ULN, or required dialysis).[2]

Select exclusion criteria: Patients with TMA due to ADAMTS13 deficiency, STEC-HUS, and genetic defect in cobalamin C metabolism; patients receiving prior PE/plasma infusion for ≥28 days; patients on chronic dialysis.[20,22]

Immediate C5 inhibition was observed by the end of the first infusion in adult patients in Study 311.[2,22]

- **100% (56/56)** of adult patients in the 26-week study demonstrated complete C5 inhibition after the first infusion[b]
- Complete inhibition of serum-free C5 was sustained throughout the 26-week treatment period in the majority (93%) of adult and pediatric patients with atypical-HUS

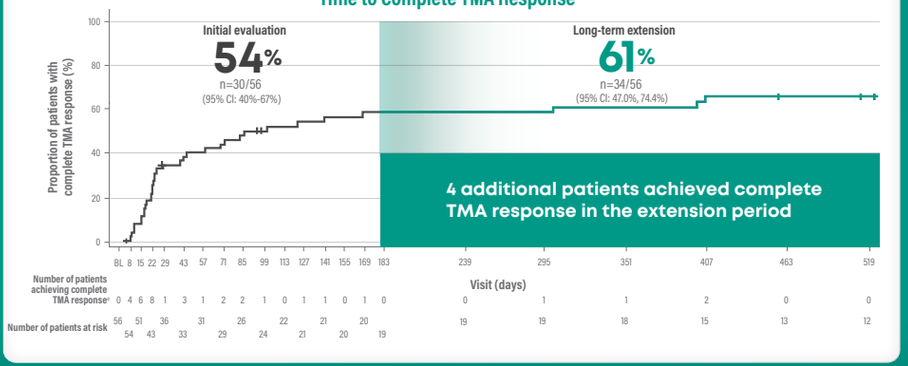
Complete TMA response was achieved in 54% (30/56) of patients taking ULTOMIRIS at 26 weeks.[2,c]

- 73% (41/56) achieved hematologic normalization
  - LDH normalization 77% (43/56)
  - Platelet normalization 84% (47/56)
- 59% (33/56) saw ≥25% improvement in SCr from baseline

Sustained disease control your patients deserve. Of the 54% of patients who achieved complete TMA response at Week 26, 100% (30/30) maintained it at Week 52.[2]

Additional responses seen beyond 6 months (26 weeks)

Time to Complete TMA Response[2,28,29,d]



ULTOMIRIS led to rapid doubling of platelets by Day 8, LDH normalization by Day 43, and progressive improvements in kidney function throughout the adult 26-week study and 52-week extension.[2,21,22]

[a]Complete TMA response was defined as normalization of hematological parameters (platelet count and LDH) and ≥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]
[b]As measured by free C5 serum concentration of <0.5 µg/mL.[2]
[c]Primary endpoint.[20]
[d]Secondary endpoint.[20]
[e]Patient achieved initial complete TMA response measurement at Day 169; however, confirmatory measurement was not achieved until the extension period (Day 239).[21]
The information presented from Study 311 is inclusive of the full study group from the pivotal trial and is not specific to patients with atypical-HUS and hypertension alone. In Study 311, 70% of patients (n=39/56) presented with hypertension at baseline.[23]

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

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.

ULTOMIRIS offered sustained C5 inhibition and an opportunity for adults to discontinue dialysis[2]

Most patients maintained or improved kidney function (n=45/47)[22]

At baseline, there were 13 patients with eGFR ≥15[22,a]

- 85% (11/13) of those patients maintained or improved their eGFR category
- 15% (2/13) of those adults declined despite treatment with ULTOMIRIS—specifically, 2 patients went from eGFR 15-29 to eGFR <15

At baseline, there were 34 patients with eGFR <15 (including dialysis)[22,b]

- 68% (23/34) of patients saw an improvement by at least 1 eGFR category
- Of the patients with eGFR <15 who improved by at least 1 eGFR category[a] (23/34), 52% (12/23) improved to eGFR ≥60


Actor portrayal

Dialysis discontinuation

At 26 Weeks

59% **17 of the 29 patients** who required dialysis at study entry discontinued dialysis by the end of available follow-up[2,b]

78% **21 of 27 patients** who were off dialysis were still not on dialysis at last available follow-up. The other 6 (22%) patients started dialysis[22]

At 52 Weeks

100% **of patients** who discontinued dialysis (17/17) stayed off dialysis through 52 weeks[21,b]

Safety profile of ULTOMIRIS in adult patients in Study 311:

The most frequent TEAEs reported in Study 311 (occurring in >15% of patients, N=58 Safety Set) were headache, diarrhea, nausea, vomiting, URTI, hypertension, arthralgia, pyrexia, edema peripheral, UTI, cough, and dyspnea. There were no meningococcal infections reported, and there were 4 deaths, deemed unrelated to the study drug, in the trial. Other TEAEs reported in Study 311 (occurring in ≥10%-15% of patients) were anemia, constipation, fatigue, gastrointestinal infection, anxiety, abdominal pain, back pain, hypokalemia, muscle spasms, pain in extremities, alopecia, and dry skin.[2,22]

[a]eGFR categories were classified based on KDIGO Guidelines for the Evaluation of Chronic Kidney Disease. eGFR values were: Category 1=≥90; Category 2=60 to 89; Category 3a=45 to 59; Category 3b=30 to 44; Category 4=15 to 29; Category 5: <15 [including dialysis]. The baseline was derived based on last available eGFR before starting treatment. Patients with both baseline and at least 1 value at post-baseline visits were included in the summary. Percentages based on number of patients with non-missing data at both baseline and post-baseline visit.

In the 311 clinical trial, CKD staging was defined by eGFR at a certain point in time. Because CKD is defined by KDIGO guidelines as abnormalities of kidney structure or function, such as low eGFR, present for a minimum of 3 months, eGFR categorization was deemed more appropriate. Stage 5 CKD is unlikely to improve.[20,24,25]

[b]Secondary endpoint.[20]

ADAMTS13=a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; atypical-HUS=atypical hemolytic uremic syndrome; C5=complement protein 5; CI=confidence interval; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; KDIGO=Kidney Disease Improving Global Outcomes; LDH=lactate dehydrogenase; PE=plasma exchange; SCr=serum creatinine; STEC-HUS=Shiga toxin *Escherichia coli*-related hemolytic uremic syndrome; TEAE=treatment-emergent adverse event; TMA=thrombotic microangiopathy; ULN=upper limit of normal; URTI=upper respiratory tract infection; UTI=urinary tract infection.

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

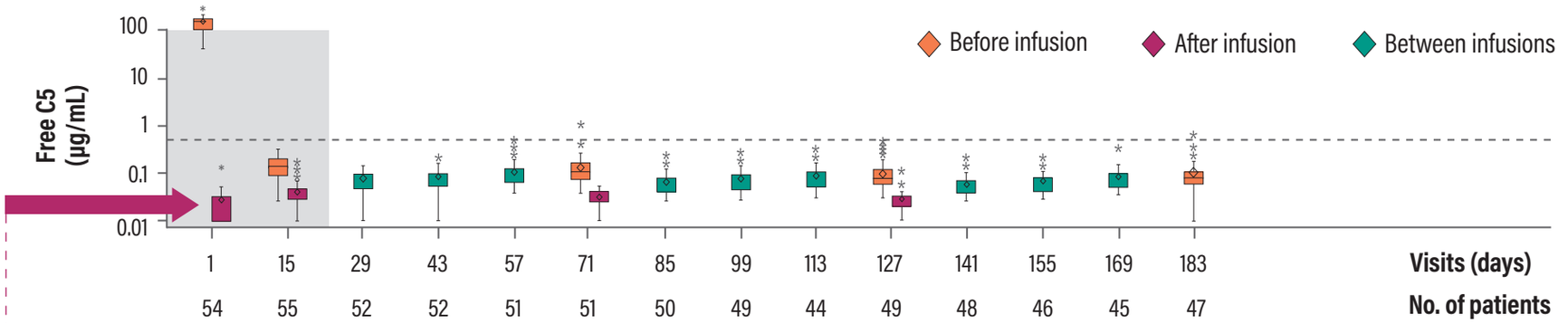
ULTOMIRIS and SOLIRIS REMS (cont'd)

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.

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

Pharmacodynamic findings showed that free C5 was immediately and completely[a] inhibited in adult patients taking ULTOMIRIS[2,22]



Adapted from Rondeau E, et al. *Kidney Int.* 2020;97:1287-1296.[22]

Box plot of free C5 vs time (semi-log scale). Pharmacodynamics of free C5 in serum concentrations from Rondeau et al, 2020. Dashed line: free C5 concentration of 0.5 µg/mL (denotes complete terminal complement inhibition). Box and whisker plot: the horizontal line in the middle of each box indicates the median, a diamond indicates the mean, and the upper and lower borders of the boxes denote the 75th and 25th percentiles, respectively. The whiskers depict the highest and lowest values within 1.5-fold the interquartile range from the lower and upper quartiles. Outliers are represented by asterisks beyond the whiskers.

The data from Study 311 showed that ULTOMIRIS inhibited C5 immediately and completely by the end of the first infusion. Complete inhibition of serum-free C5 (concentration of less than 0.5 µg/mL) was observed by the end of the first ULTOMIRIS infusion and sustained throughout the entire 26-week treatment period in the majority (93%) of adult and pediatric patients with atypical-HUS.[2,22,b]

- **>99.5%** of all free C5 serum samples in adult patients showed complete inhibition of C5 throughout the 6-month study period with ULTOMIRIS[22,a]

[a]Defined as a free serum C5 concentration <0.5 µg/mL.[2,22]
[b]Data for pediatric patients were consistent with those for adults.[26]

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

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.

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

ULTOMIRIS: the patient preferred treatment for atypical-HUS based on survey results

In a survey of adult US patients (N=50) with confirmed atypical-HUS who had previously received short-acting therapy with eculizumab and ≥3 doses of ULTOMIRIS[27,a,b]:

Adult patient-reported survey: proportion of patients (%) who preferred ULTOMIRIS over eculizumab regarding specific parameters[27,c]					Adult patients were asked about how ULTOMIRIS impacted them[27,d]
Frequency of infusions	Travel/ vacation	Benefit to your quality of life	Planning social activities	Length of time to receive infusion	The frequency of my infusions did not disrupt my life
100%	**98%**	**86%**	**86%**	**74%**	**96%**
n/N=50/50	n/N=48/49	n/N=43/50	n/N=42/49	n/N=37/50	n/N=48/50
					Based on their experience during their treatment with SOLIRIS and after switching to ULTOMIRIS

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.[27]

[a]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.[27]

[b]Eculizumab is infused every 2 weeks after 5 weeks of initial loading dose for adults. ULTOMIRIS is infused every 4 or 8 weeks after 2 weeks of initial loading dose, per weight-based dosing.[2,28]

[c]Percentages represent the percent of patients who preferred ULTOMIRIS vs preferring eculizumab/having no preference.[27]

[d]Percentages represent the percent of patients who agreed "quite a bit/somewhat/very much" with the survey question or agreed "not at all/a little bit" to the inverse of the question presented here.[27]

Fewer visits[29]	Less patient burden[29]
Fewer infusions[21]	Less likelihood of exposure to infection[21]
Reduced infusion time[29,f]	Less time spent at the hospital[29]

Lower frequency of infusions (about 6-7/year)[e,f] reduces patient exposure to infusion-associated risks and adverse events associated with repeated venous access[2,21,30,31]

These outcomes are not specific to ULTOMIRIS alone.

[e]Eculizumab is infused every 2 weeks after 5 weeks of initial loading dose for adults. ULTOMIRIS is infused every 4 or 8 weeks after 2 weeks of initial loading dose, per weight-based dosing.[2,28]

[f]Dosing schedules and infusion times vary depending on body weight and concentration administered. 6-7 ULTOMIRIS maintenance doses per year is based on patients ≥20 kg.[2]

Atypical-HUS=atypical hemolytic uremic syndrome; C5=complement component 5.

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

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.

Case Study: Jerry
Management of atypical-HUS in a patient with MHT

Overview: 53 y/o male presented to ED from clinic due to severe hypertension (BP 210/120 mmHg)

Jerry

Actor portrayal

Family History

- HTN (both parents)
- Aneurysm (father - deceased)

HPI

- Reported intermittent headaches for 2 weeks – now constant and associated with fatigue and nausea
- Self-treated with NSAID as needed

Initial Presentation

- Vitals: BP 210/106 mmHg; Heart Rate: 90 bpm
- Physical examination: + pallor; 2+ bilateral lower extremity swelling

Hypothetical patient case.

Initial Labs in the ED

		Lab values at presentation	Reference values[12]
Complete Blood Count	Hemoglobin (g/dL)	8.4	14-17
	Hematocrit (%)	24.4	41-51
	White blood cell count (x 10^3 cells/mcL)	10.6	4.5-11
	Platelet count (x 10^3 mcL)	126	150-350
Comprehensive Metabolic Panel	Sodium (mEq/L)	140	136-145
	Potassium (mEq/L)	5.5	3.5-5
	Chloride (mEq/L)	110	98-106
	Bicarbonate (mEq/L)	22	23-28
	BUN (mg/dL)	39	8-20
	Serum creatinine (mg/dL)	3.2	0.7-1.2
Liver enzymes	AST (U/L)	36	<35
	ALT (U/L)	29	<35
Urinalysis	Sp Gr 1.024, 3+ protein, 2+ blood, 5-10 RBCs and no WBCs		

At Day 0, Jerry was transferred to ICU and started on IV antihypertensive medication to maintain SBP of 160-180.

By Day 1, Jerry was transitioned to oral antihypertensive medications, but BP remained elevated and renal function continued to worsen.

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

Monitoring Disease Manifestations after ULTOMIRIS Discontinuation (cont'd)

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.

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

Case Study: Jerry (Cont'd)

On Day 5, ADAMTS13 activity levels were ordered.
- Plasmapheresis and hemodialysis were initiated

A renal biopsy was performed on Day 7, and preliminary results showed RPGN.
- Jerry was started on a steroid and immunosuppressant
- Light microscopy showed TMA and secondary vascular changes

On Day 8, ADAMTS13 activity levels were 77%. With TTP ruled out, a diagnosis of atypical-HUS was assumed.
- Plasmapheresis was discontinued
- Jerry received meningococcal vaccine

On Day 9, treatment with eculizumab 900 mg was initiated with prophylactic antibiotic use in accordance with PI and ACIP guidelines.

By Day 16, platelet count and LDH levels had improved enough to allow for discharge.
- Second dose of eculizumab was administered
- Jerry was discharged from the hospital with outpatient follow-up scheduled

Post-discharge:
- Dialysis was discontinued on Day 19
- Genetic testing was performed and revealed Complement Factor H VUS mutation

Jerry was switched to ULTOMIRIS at Day 23 in accordance with PI.
- Renal function improved to baseline by 12 months and remained in remission for 6 months thereafter
- Jerry was on therapy for 12 months. Data for the first 120 days is shown on the next page

ACIP=Advisory Committee on Immunization Practices; ADAMTS13=a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; ALT=alanine transaminase; AST=aspartate aminotransferase; atypical-HUS=atypical hemolytic uremic syndrome; BP=blood pressure; bpm=beats per minute; BUN=blood urea nitrogen; ED=emergency department; HPI=history of present illness; HTN=hypertension; ICU=intensive care unit; IV=intravenous; LDH=lactate dehydrogenase; MHT=malignant hypertension; NSAID=nonsteroidal anti-inflammatory drug; PI=prescribing information; RBC=red blood cell; RPGN=rapidly progressive glomerulonephritis; SBP=systolic blood pressure; Sp Gr=specific gravity; TMA=thrombotic microangiopathy; TTP=thrombotic thrombocytopenic purpura; VUS=variant of uncertain significance; WBC=white blood cell.

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

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.

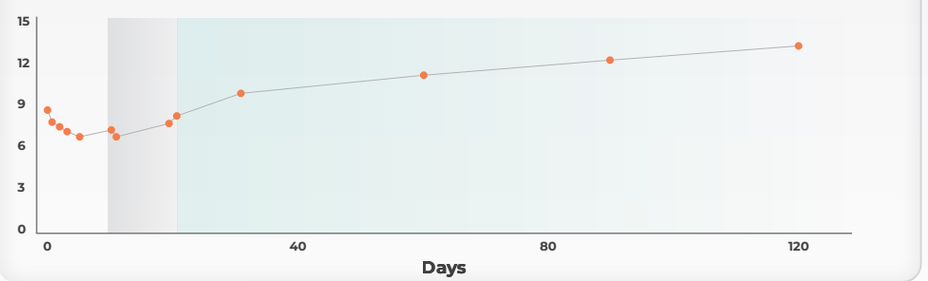
ADVERSE REACTIONS

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.

Case Study: Jerry (Cont'd)
Laboratory values on ULTOMIRIS

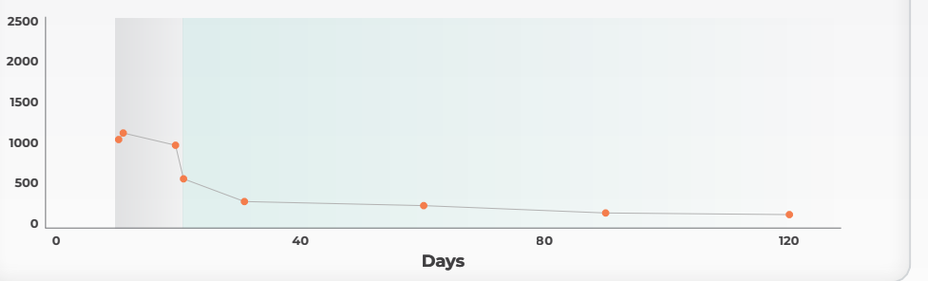
Hb (g/dL)



Reference Values: 14-17[32]

Treated with eculizumab | Switched to ULTOMIRIS

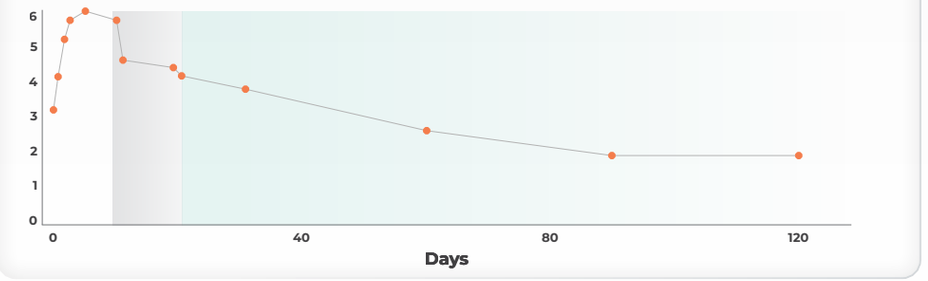
LDH (units/L)



Reference Values: 60-160[32]

Treated with eculizumab | Switched to ULTOMIRIS

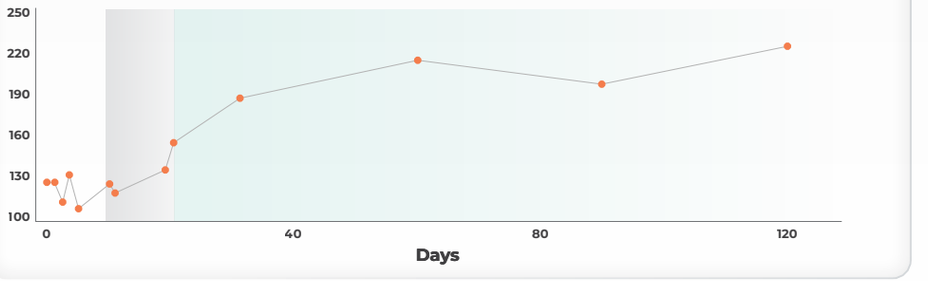
SCr (mg/dL)



Reference Values: 0.7-1.2[32]

Treated with eculizumab | Switched to ULTOMIRIS

Plts (10^3/mcL)



Reference Values: 150-350[32]

Treated with eculizumab | Switched to ULTOMIRIS

SELECT IMPORTANT SAFETY INFORMATION

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.

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

Alexion: a long-standing history of commitment to supporting healthcare professionals and their patients

For Patients

ONESOURCE®
Personalized Patient Support from Alexion

We created OneSource™ to support your patients every step of the way

OneSource is a complimentary, personalized patient support program available for patients, families, and caregivers facing complement-mediated diseases to help them start and stay on the treatment as prescribed.

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

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 patients eligible to be reimbursed by government insurance programs[b] 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** or **OneSource@Alexion.com** for more information on patient eligibility

[a]Based on typical commercial patient out-of-pocket deductible limits. Additional terms and conditions apply. Please contact OneSource with additional questions.

[b]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.

Atypical-HUS=atypical hemolytic uremic syndrome; COVID-19=Coronavirus disease 2019; FDA=Food and Drug Administration; Hb=hemoglobin; ICD-10=International Classification of Diseases, Tenth Revision; LDH=lactate dehydrogenase; Plts=platelets; SCr=serum creatinine.

For HCPs

ALEXION ACCESS NAVIGATOR

Alexion Access Navigator

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

Utilize atypical-HUS ICD-10 codes to avoid coverage challenges

D59.32 Hereditary hemolytic uremic syndrome

Atypical hemolytic uremic syndrome with an identified genetic cause

Code also, if applicable

- **Defects in the complement system (D84.1)**
- **Methylmalonic acidemia (E71.120)**

D59.39 Other hemolytic uremic syndrome

Atypical (nongenetic) hemolytic uremic syndrome

Secondary hemolytic uremic syndrome

Code first, if applicable, any associated:

- **COVID-19 (U07.1)**
- **Complications of liver transplant (T86.4-)**
- **Complications of kidney transplant (T86.1-)**
- **Complications of heart transplant (T86.2-)**

Code also, if applicable, any associated condition, such as:

- **Hypertensive emergency (I16.1)**
- **Systemic lupus erythematosus (M32.-)**
- **Malignant neoplasm (C00-C96)**

Use Additional code, if applicable, for adverse effect to identify drug **(T36-T50 with fifth or sixth character 5)**

Rapidly identify TMA and diagnosis of atypical-HUS for your patients with mHTN[3,4,12]

mHTN may be a more common trigger of atypical-HUS than realized.

In a retrospective study of hospitalized patients with mHTN (N=199)[11,a]:

of patients with mHTN had TMA

and of them

had atypical-HUS at baseline

Consider ULTOMIRIS as a first-line treatment for your patients with atypical-HUS.[2,22]

IMMEDIATE
C5 INHIBITION

Immediate and complete inhibition of C5[b] was observed by the end of the first infusion of ULTOMIRIS by 100% of adult patients.[2,21,22]

COMPLETE[c]
TMA RESPONSE

54% (30/56; 95% CI: 40%-67%) of adult patients achieved complete TMA response at Week 26, with more patients achieving complete response with longer follow-up (61% of adults with median follow-up of 76.7 weeks).[2,20,21]

SUSTAINED[d]
DISEASE CONTROL

ULTOMIRIS demonstrated sustained efficacy and safety achieved during the 26-week trial and through the long-term extension period.[21]

Prompt initiation of C5 inhibition has been shown to resolve TMAs and maintain or improve kidney function in the majority of patients.[12,17,22,33]

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

[a]Retrospective cohort analysis of hospitalized patients diagnosed with mHTN (N=199) from 2000-2020 in 8 nephrology departments in Spain.[11]

[b]As measured by free C5 serum concentration of <0.5 mcg/mL.[2]

[c]The primary endpoint of complete TMA response was defined as normalization of hematological parameters (platelet count and LDH) and ≥25% improvement in serum creatinine (SCr) 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]

[d]Sustained disease control and efficacy as measured by patients maintaining complete TMA response, defined as normalization of hematologic parameters (platelet count and LDH) and ≥25% improvement in SCr from baseline achieved during the initial 26-week trial, through the long-term study extension. Sustained safety as demonstrated by no unexpected AEs from the end of the initial evaluation period to the extension period of the adult study.[21]

AE=adverse event; atypical-HUS=atypical hemolytic uremic syndrome; C5=complement component 5; LDH=lactate dehydrogenase; mHTN=malignant hypertension; TMA=thrombotic microangiopathy.

References: 1. Data on file. Atypical-HUS market access dashboard. Alexion Pharmaceuticals, Inc.; 2023. **2.** ULTOMIRIS. Prescribing Information. Alexion Pharmaceuticals, Inc. **3.** Boulestreau R, et al. *J Am Heart Assoc*. 2022;11:e023397. **4.** Laurence J, et al. *Clin Adv Hematol Oncol*. 2016;14 Suppl 11(11):2-15. **5.** Asif A, et al. *J Nephrol*. 2017;30:347-362. **6.** Timmermans S, et al. *Kidney Int*. 2017;91(6):1420-1425. **7.** Halimi JM, et al. *BMC Nephrology*. 2022;23(1):39. **8.** Whelton PK, et al. *Hypertension*. 2018;71:e13-e115. **9.** Timmermans S, et al. *Kidney Int Rep*. 2021;6(4):1099-1109. **10.** Halimi JM, et al. *Journal of Nephrology*. 2023;36:817-828. **11.** Cavero T, et al. *Nephrol Dial Transplant*. 2023;38:1217-1226. **12.** Azoulay E, et al. *Chest*. 2017;152(2):424-434. **13.** Schaefer F, et al. *Kidney Int*. 2018;94:408-418. **14.** El Karoui K, et al. *Haematologica*. 2019;104(12):2501-2511. **15.** Kim YJ. *Kidney Res Clin Pract*. 2022;41(5):524-532. **16.** Fakhouri F, et al. *The Lancet*. 2017;390(10095):948. **17.** Vande Walle J, et al. *J Nephrol*. 2017;30:127-137. **18.** Campistol JM, et al. *Nefrologia*. 2015;35(5):421-447. **19.** Lusco MA, et al. *Am J Kidney Dis*. 2016;68(6):e33-e34. **20.** Data on file. [ALXN1210-aHUS-311CSR]. **21.** Barbour T, et al. *Kidney Int Rep*. (article and supplement) 2021;6(6):1603-1613. **22.** Rondeau E, et al. *Kidney Int*. 2020;97(6):1287-1296. **23.** Data on file. [ALXN1210-aHUS-311CSR Demographics and Baseline Characteristics]. **24.** Chen TK, et al. *JAMA*. 2019;322(13):1294-1304. **25.** International Society of Nephrology. *KDIGO 2024 Clinical Guideline for the Evaluation and Management of Chronic Kidney Disease*. 2024;105(45):S117-S314. **26.** Ariceta G, et al. *Kidney Int*. 2021;100(1):225-237. **27.** Mauch TJ, et al. *J Comp Eff Res*. 2023;12(9):e230036. **28.** SOLIRIS. Prescribing Information. Alexion Pharmaceuticals, Inc. **29.** Levy AR, et al. *J Med Econ*. 2022;25(1):249-259. **30.** Syed YY. *Drugs*. 2021;81(5):587-594. **31.** Dixon BP, Sabus A. *J Clin Pharm Ther*. 2022;47(7):1081-1087. **32.** Merck Manual. Merck & Co. Inc.; 2022. **33.** Legendre CM, et al. *N Engl J Med*. 2013;368(23):2169-2181.

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.

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®
AstraZeneca Rare Disease