Update on US regulatory review of ULTOMIRIS® in NMOSD

September 6, 2023

September 6, 2023 – The US Food and Drug Administration (FDA) has issued a complete response letter (CRL) regarding the supplemental Biologics License Application (sBLA) for long-acting C5 complement inhibitor ULTOMIRIS® (ravulizumab-cwvz) for the treatment of adult patients with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody positive (Ab+).

The CRL did not request additional analysis or reanalysis of the Phase III CHAMPION-NMOSD trial data included in the sBLA submission and did not raise concerns about the efficacy or safety data from the trial.[1]

The FDA requested modifications to enhance the ULTOMIRIS Risk Evaluation and Mitigation Strategy (REMS) to further validate patients' meningococcal vaccination status or prophylactic administration of antibiotics prior to treatment.

Alexion, AstraZeneca Rare Disease is working closely with the FDA regarding next steps for the REMS modifications and remains committed to bringing ULTOMIRIS to people living with NMOSD in the US as quickly as possible.

ULTOMIRIS is currently approved for the treatment of certain adults with NMOSD in the European Union (EU), Japan and other countries.

ULTOMIRIS is approved by the FDA for the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) Ab+, and certain adults and children with paroxysmal nocturnal hemoglobinuria (PNH) or atypical hemolytic uremic syndrome (aHUS).

INDICATION(S) & IMPORTANT SAFETY INFORMATION for ULTOMIRIS® (ravulizumab-cwvz)

What is ULTOMIRIS?

ULTOMIRIS is a prescription medicine used to treat:

- adults and children 1 month of age and older with a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH).
- adults and children 1 month of age and older with a disease called atypical Hemolytic Uremic Syndrome (aHUS). ULTOMIRIS is not used in treating people with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).
- adults with a disease called generalized Myasthenia Gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody positive.
- adults with PNH or aHUS when administered subcutaneously (under your skin).

It is not known if ULTOMIRIS is safe and effective in children younger than 1 month of age.

It is not known if ULTOMIRIS is safe and effective for the treatment of gMG in children.

Subcutaneous administration of ULTOMIRIS has not been evaluated and is not approved for use in children.

IMPORTANT SAFETY INFORMATION

What is the most important information I should know about ULTOMIRIS?

ULTOMIRIS is a medicine that affects your immune system and can lower the ability of your immune system to fight infections.

- ULTOMIRIS increases your chance of getting serious and life-threatening meningococcal infections that may quickly become life-threatening and cause death if not recognized and treated early.

1. You must receive meningococcal vaccines at least 2 weeks before your first dose of ULTOMIRIS if you are not vaccinated.
2. If your healthcare provider decided that urgent treatment with ULTOMIRIS is needed, you should receive meningococcal vaccination as soon as possible.
3. If you have not been vaccinated and ULTOMIRIS therapy must be initiated immediately, you should also receive 2 weeks of antibiotics with your vaccinations.
4. If you had a meningococcal vaccine in the past, you might need additional vaccination. Your healthcare provider will decide if you need additional vaccination.
5. Meningococcal vaccines reduce but do not prevent all meningococcal infections. Call your healthcare provider or get emergency medical care right away if you get any of these signs and symptoms of a meningococcal infection: headache with nausea or vomiting, headache and fever, headache with a stiff neck or stiff back, fever, fever and a rash, confusion, muscle aches with flu-like symptoms and eyes sensitive to light.

Your healthcare provider will give you a Patient Safety Card about the risk of meningococcal infection. Carry it with you at all times during treatment and for 8 months after your last ULTOMIRIS dose. It is important to show this card to any healthcare provider or nurse to help them diagnose

and treat you quickly.

ULTOMIRIS is only available through a program called the ULTOMIRIS REMS. Before you can receive ULTOMIRIS, your healthcare provider must: enroll in the ULTOMIRIS REMS program; counsel you about the risk of meningococcal infection; give you information and a Patient Safety Card about the symptoms and your risk of meningococcal infection (as discussed above); and make sure that you are vaccinated with a meningococcal vaccine, and if needed, get revaccinated with the meningococcal vaccine. Ask your healthcare provider if you are not sure if you need to be revaccinated.

ULTOMIRIS may also increase the risk of other types of serious infections. Make sure your child receives vaccinations against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) if treated with ULTOMIRIS. Call your healthcare provider right away if you have any new signs or symptoms of infection.

Who should not receive ULTOMIRIS?

Do not receive ULTOMIRIS if you have a meningococcal infection or have not been vaccinated against meningococcal infection unless your healthcare provider decides that urgent treatment with ULTOMIRIS is needed.

Before you receive ULTOMIRIS, tell your healthcare provider about all of your medical conditions, including if you: have an infection or fever, are pregnant or plan to become pregnant, and are breastfeeding or plan to breastfeed. It is not known if ULTOMIRIS will harm your unborn baby or if it passes into your breast milk. You should not breastfeed during treatment and for 8 months after your final dose of ULTOMIRIS.

Tell your healthcare provider about all the vaccines you receive and medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements which could affect your treatment.

If you have PNH and you stop receiving ULTOMIRIS, your healthcare provider will need to monitor you closely for at least 16 weeks after you stop ULTOMIRIS. Stopping ULTOMIRIS may cause breakdown of your red blood cells due to PNH. Symptoms or problems that can happen due to red blood cell breakdown include: drop in your red blood cell count, tiredness, blood in your urine, stomach-area (abdomen) pain, shortness of breath, blood clots, trouble swallowing, and erectile dysfunction (ED) in males.

If you have aHUS, your healthcare provider will need to monitor you closely for at least 12 months after stopping treatment for signs of worsening aHUS or problems related to a type of abnormal clotting and breakdown of your red blood cells called thrombotic microangiopathy (TMA). Symptoms or problems that can happen with TMA may include: confusion or loss of consciousness, seizures, chest pain (angina), difficulty breathing and blood clots or stroke.

ULTOMIRIS can cause serious side effects including allergic reactions to acrylic adhesive. Allergic reactions to the acrylic adhesive may happen with your subcutaneous ULTOMIRIS treatment. If you have an allergic reaction during the delivery of subcutaneous ULTOMIRIS, remove the on-body injector and get medical help right away. Your healthcare provider may treat you with medicines to help prevent or treat allergic reaction symptoms as needed.

What are the possible side effects of ULTOMIRIS?

ULTOMIRIS can cause serious side effects including infusion-related reactions. Symptoms of an infusion-related reaction with ULTOMIRIS may include lower back pain, tiredness, feeling faint, discomfort in your arms or legs, bad taste, or drowsiness. Stop treatment of ULTOMIRIS and tell your healthcare provider or nurse right away if you develop these symptoms, or any other symptoms during your ULTOMIRIS infusion that may mean you are having a serious infusion reaction, including: chest pain, trouble breathing or shortness of breath, swelling of your face, tongue, or throat, and feel faint or pass out.

The most common side effects of ULTOMIRIS in people treated for PNH are upper respiratory tract infection and headache.

The most common side effects of ULTOMIRIS in people treated for aHUS are upper respiratory tract infection, diarrhea, nausea, vomiting, headache, high blood pressure and fever.

The most common side effects of ULTOMIRIS in people with gMG are diarrhea and upper respiratory tract infections.

The most common side effects of subcutaneous administration of ULTOMIRIS in adults treated for PNH and aHUS are local injection site reactions.

Tell your healthcare provider about any side effect that bothers you or that does not go away. These are not all the possible side effects of ULTOMIRIS. For more information, ask your healthcare provider or pharmacist. Call your healthcare provider right away if you miss an ULTOMIRIS infusion or for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Read the Instructions for Use that comes with subcutaneous ULTOMIRIS for instructions about the right way to prepare and give your subcutaneous ULTOMIRIS injections through an on-body injector.

Please see the accompanying full Prescribing Information and Medication Guide for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis. Please see the accompanying Instructions for Use for the ULTOMIRIS On Body Delivery System.

Notes

NMOSD

NMOSD is a rare disease in which the immune system is inappropriately activated to target healthy tissues and cells in the central nervous system (CNS).[2,3] Approximately three-quarters of people with NMOSD are anti-AQP4 Ab+, meaning they produce antibodies that bind to a specific protein, aquaporin-4 (AQP4).[4] This binding can inappropriately activate the complement system, which is part of the immune system and is essential to the body's defense against infection, to destroy cells in the optic nerve, spinal cord and brain. [2,5,6]

It most commonly affects women and begins in the mid-30s. Men and children may also develop NMOSD, but it is even more rare.[7,8] People with NMOSD may experience vision problems, intense pain, loss of bladder/bowel function, abnormal skin sensations (e.g., tingling, prickling or sensitivity to heat/cold) and impact on coordination and/or movement.[9-13] Most people living with NMOSD experience unpredictable relapses, also known as attacks. Each relapse can result in cumulative disability including vision loss, paralysis and sometimes premature death.[10,11,14] NMOSD is a distinct disease from other CNS diseases, including multiple sclerosis. The journey to diagnosis can be long, with the disease sometimes misdiagnosed.[15-17]

CHAMPION-NMOSD
CHAMPION-NMOSD is a global Phase III, open-label, multicenter trial evaluating the safety and efficacy of ULTOMIRIS in adults with NMOSD. The trial enrolled 58 patients across North America, Europe, Asia-Pacific and Japan. Participants were required to have a confirmed NMOSD diagnosis with a positive anti-AQP4 antibody test, at least one attack or relapse in the twelve months prior to the screening visit, an Expanded Disability Status Scale Score of 7 or less and body weight of at least 40 kilograms at trial entry. Participants could stay on stable supportive immunosuppressive therapy for the duration of the trial.[18]

Due to the potential long-term functional impact of NMOSD relapses and available effective treatment options, a direct placebo comparator arm was precluded for ethical reasons. The active treatment was compared to an external placebo arm from the pivotal SOLIRIS PREVENT clinical trial.

Over a median treatment duration of 73 weeks, all enrolled patients received a single weight-based loading dose of ULTOMIRIS on Day 1, followed by regular weight-based maintenance dosing beginning on Day 15, every eight weeks. The primary endpoint was time to first on-trial relapse, as confirmed by an independent adjudication committee. The end of the primary treatment period could have occurred either when all patients completed or discontinued prior to the Week 26 visit and two or more adjudicated relapses were observed, or when all patients completed or discontinued prior to the Week 50 visit if fewer than two adjudicated relapses were observed. In the trial, there were zero adjudicated relapses, so the end of the primary treatment period occurred when the last enrolled participant completed the 50-week visit.

Patients who completed the primary treatment period were eligible to continue into a long-term extension period, which is ongoing.

ULTOMIRIS
ULTOMIRIS (ravulizumab-cwvz), the first and only long-acting C5 complement inhibitor, provides immediate, complete and sustained complement inhibition. The medication works by inhibiting the C5 protein in the terminal complement cascade, a part of the body's immune system. When activated in an uncontrolled manner, the complement cascade over-responds, leading the body to attack its own healthy cells. ULTOMIRIS is administered intravenously every eight weeks in adult patients, following a loading dose.

ULTOMIRIS is approved in the US, EU and Japan for the treatment of certain adults with generalized myasthenia gravis.

ULTOMIRIS is also approved in the US, EU and Japan for the treatment of certain adults with paroxysmal nocturnal hemoglobinuria (PNH) and for certain children with PNH in the US and EU.

Additionally, ULTOMIRIS is approved in the US, EU and Japan for certain adults and children with atypical hemolytic uremic syndrome to inhibit complement-mediated thrombotic microangiopathy.

Further, ULTOMIRIS is approved in the EU and Japan for the treatment of certain adults with neuromyelitis optica spectrum disorder (NMOSD).

As part of a broad development program, ULTOMIRIS is being assessed for the treatment of additional hematology and neurology indications.

Alexion

Alexion, AstraZeneca Rare Disease, is the group within AstraZeneca focused on rare diseases, created following the 2021 acquisition of Alexion Pharmaceuticals, Inc. As a leader in rare diseases for more than 30 years, Alexion is focused on serving patients and families affected by rare diseases and devastating conditions through the discovery, development and commercialization of life-changing medicines. Alexion focuses its research efforts on novel molecules and targets in the complement cascade and its development efforts on hematology, nephrology, neurology, metabolic disorders, cardiology and ophthalmology. Headquartered in

Boston, Massachusetts, Alexion has offices around the globe and serves patients in more than 50 countries. For more information, please visit www.alexion.com.

AstraZeneca
AstraZeneca (LSE/STO/Nasdaq: AZN) is a global, science-led biopharmaceutical company that focuses on the discovery, development, and commercialization of prescription medicines in Oncology, Rare Diseases, and BioPharmaceuticals, including Cardiovascular, Renal & Metabolism, and Respiratory & Immunology. Based in Cambridge, UK, AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide. Please visit astrazeneca.com and follow the Company on social media @AstraZeneca.

Media Inquiries

Alexion Media Mailbox: media@alexion.com

References

1. Pittock SJ, et al. Efficacy and safety of ravulizumab in adults with anti-aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder: outcomes from the phase 3 CHAMPION-NMOSD trial. Oral Presentation at: American Academy of Neurology Annual Meeting, April 23, 2023; Presentation S5.002.
2. Wingerchuk DM, et al. The spectrum of neuromyelitis optica. *Lancet Neurol*. 2007;6(9):805-815.
3. Wingerchuk DM. Diagnosis and treatment of neuromyelitis optica. *Neurologist*. 2007;13(1):2-11.
4. Wingerchuk DM, et al. The clinical course of neuromyelitis optica (Devic's syndrome). *Neurology*. 1999;53(5):1107-1114.
5. Cossburn M, et al. The Prevalence of Neuromyelitis Optica in South East Wales. *Eur J Neurol*. 2012;19(4): 655-659.

6. Papadopoulos MC, et al. Treatment of neuromyelitis optica: state-of-the-art and emerging therapies. *Nat Rev Neurol*. 2014;10(9):493.
7. Takata K, et al. Aquaporins: water channel proteins of the cell membrane. *Prog Histochem Cytochem*. 2004;39(1):1-83.
8. Mori M, et al. Worldwide prevalence of neuromyelitis optica spectrum disorders. *J Neurol Neurosurg Psychiatry*. 2018;89(6):555-556.
9. Hamid SHM, et al. What proportion of AQP4-IgG-negative NMO spectrum disorder patients are MOG-IgG positive? A cross sectional study of 132 patients. *J Neurol*. 2017;264(10):2088-2094.
10. Wingerchuk DM, Weinshenker BG. Neuromyelitis optica. *Curr Treat Options Neurol*. 2008;10(1):55-66.
11. Kitley J, et al. Prognostic factors and disease course in aquaporin-4 antibody-positive patients with neuromyelitis optica spectrum disorder from the United Kingdom and Japan. 2012;135(6):1834-1849.
12. Quek AML, et al. Effects of age and sex on aquaporin-4 autoimmunity. *Arch Neurol* 2012;69:1039–43.
13. Tüzün E, et al. Enhanced complement consumption in neuromyelitis optica and Behcet's disease patients. *J Neuroimmunol*. 2011;233(1-2):211-215.
14. Jarius S, et al. Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: a multicentre study of 175 patients. *J Neuroinflammation.* 2012;9:14.
15. Jarius S, Wildemann B. The History of Neuromyelitis Optica. *J Neuroinflammation*. 2013;10, 797.
16. Kuroda H, et al. Increase of complement fragment C5a in cerebrospinal fluid during exacerbation of neuromyelitis optica. *J Neuroimmunol*. 2013;254(1-2):178-182.
17. Mealy MA, et al. Assessment of Patients with Neuromyelitis Optica Spectrum Disorder Using the EQ-5D. *Int J MS Care*. 2019;21(3), 129-134.
18. ClinicalTrials.gov. An Efficacy and Safety Study of Ravulizumab in Adult Participants With NMOSD. NCT Identifier: NCT04201262. Available here. Accessed August 2023.