ULTOMIRIS® (ravulizumab-cwvz) approved in the US for the treatment of adults with neuromyelitis optica spectrum disorder (NMOSD)

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First and only long-acting C5 complement inhibitor offers patients with AQP4 Ab+ NMOSD the potential to live relapse-free

Unprecedented relapse risk reduction observed in CHAMPION-NMOSD trial underscores how ULTOMIRIS may redefine patient journey for rare neurological disease

ULTOMIRIS® (ravulizumab-cwvz) has been approved in the United States (US) as the first and only long-acting C5 complement inhibitor for the treatment of adult patients with anti-aquaporin-4 (AQP4) antibody-positive (Ab+) neuromyelitis optica spectrum disorder (NMOSD).[1]

The approval by the US Food and Drug Administration (FDA) was based on positive results from the CHAMPION-NMOSD Phase III trial, which were published in the *Annals of Neurology*.[2] In the trial, ULTOMIRIS was compared to an external placebo arm from the pivotal SOLIRIS® PREVENT clinical trial.

ULTOMIRIS met the primary endpoint of time to first on-trial relapse as confirmed by an independent adjudication committee. Zero relapses were observed among ULTOMIRIS patients with a median treatment duration of 73 weeks (relapse risk reduction: 98.6%, hazard ratio (95% CI): 0.014 (0.000, 0.103), $p<0.0001$).[2]

NMOSD is a rare and debilitating autoimmune disease that affects the central nervous system (CNS), including the spine and optic nerves.[3-5] Most people living with NMOSD experience unpredictable relapses, characterized by a new onset of neurologic symptoms or worsening of existing neurologic symptoms, which tend to be severe and recurrent and may result in permanent disability.[6-8] The diagnosed prevalence of adults with NMOSD in the US is estimated at approximately 6,000.[9-11]

Sean J. Pittock, MD, Director of Mayo Clinic's Center for Multiple Sclerosis and Autoimmune Neurology and of Mayo's Neuroimmunology Laboratory and lead primary investigator in the CHAMPION-NMOSD trial, said: “C5 inhibition has been proven to offer efficacy in reducing the risk of NMOSD relapses by blocking the complement system, a part of the immune system, from attacking healthy cells in the spinal cord, optic nerve and brain. With today’s FDA approval, patients now have the option of a long-acting C5 inhibitor treatment that showed zero relapses in the pivotal CHAMPION-NMOSD trial, supporting the primary goal of relapse prevention in treating NMOSD.”

Marc Dunoyer, Chief Executive Officer, Alexion, said: “Alexion has been at the forefront of innovation in NMOSD, striving to offer patients a future without fear of life-altering or even fatal relapses. Building on the established efficacy of C5 inhibition for people living with AQP4 Ab+ NMOSD, we are proud to deliver a transformative, long-acting treatment option that has the potential to eliminate relapses with a convenient dosing schedule every eight weeks. We are grateful to the NMOSD community for their ongoing collaboration and input, which enables us to advance science for rare diseases.”

Overall, the safety and tolerability of ULTOMIRISin the CHAMPION-NMOSD trial were consistent with previous clinical studies and real-world use, and no new safety signals were observed. The most common adverse events (AEs) were COVID-19, headache, back pain, arthralgia and urinary tract infection.[2]

ULTOMIRIS is also approved for certain adults with NMOSD in Japan and the European Union (EU). Regulatory reviews are ongoing in additional countries.

INDICATION(S) & IMPORTANT SAFETY INFORMATION

INDICATION(S)
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 a disease called Neuromyelitis Optica Spectrum Disorder (NMOSD) who are anti-aquaporin 4 (AQP4) antibody positive.

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 or NMOSD 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 may lower the ability of your immune system to fight infections.

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

1. You must complete or update meningococcal vaccine(s) at least 2 weeks before your first dose of ULTOMIRIS.
2. If you have not completed your meningococcal vaccines and ULTOMIRIS must be started right away, you should receive the required vaccine(s) as soon as possible.
3. If you have not been vaccinated and ULTOMIRIS must be started right away, you should also receive antibiotics for as long as your healthcare provider tells you.
4. If you had a meningococcal vaccine in the past, you might need additional vaccines before starting ULTOMIRIS. Your healthcare provider will decide if you need additional meningococcal vaccines.
5. Meningococcal vaccines 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**: fever, fever with high heart rate, headache and fever, confusion, muscle aches with flu-like symptoms, fever and a rash, headache with nausea or vomiting, headache with a stiff neck or stiff back, or eyes sensitive to light.

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

ULTOMIRIS is only available through a program called the ULTOMIRIS and SOLIRIS Risk Evaluation and Mitigation Strategy (REMS). Before you can receive ULTOMIRIS, your healthcare provider must: enroll in the REMS program; counsel you about the risk of serious meningococcal infections; give you information about the signs and symptoms of serious meningococcal infection; make sure that you are vaccinated against serious infections caused by meningococcal bacteria, and that you receive antibiotics if you need to start ULTOMIRIS right away and are not up to date on your vaccines; give you a **Patient Safety Card** about your risk of meningococcal infection.

ULTOMIRIS may also increase the risk of other types of serious infections, including *Streptococcus pneumoniae, Haemophilus influenzae,* and *Neisseria gonorrhoeae*. Your child should receive vaccines against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) if treated with ULTOMIRIS. Certain people may be at risk of serious infections with gonorrhea.

Who should not receive ULTOMIRIS?
Do not receive ULTOMIRIS if you have a serious meningococcal infection when you are starting ULTOMIRIS.

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.

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, abdominal pain, muscle spasms, changes in blood pressure, tiredness, feeling faint, shaking chills (rigors), discomfort in your arms or legs, bad taste, or drowsiness. Stop treatment of ULTOMIRIS and tell your healthcare provider right away if you develop these symptoms, or any other symptoms during your ULTOMIRIS infusion that may mean you are having a serious infusion-related 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 ULTOMIRIS in people with NMOSD are COVID-19 infection, headache, back pain, urinary tract infection, and joint pain (arthralgia).

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.

Please see the accompanying full Prescribing Information and Medication Guide for ULTOMIRIS, including Boxed WARNING regarding serious meningococcal infections.

Notes

NMOSD

NMOSD is a rare disease in which the immune system is inappropriately activated to target healthy tissues and cells in the CNS.[3,4] Approximately three-quarters of people with NMOSD are anti-AQP4 Ab+, meaning they produce antibodies that bind to a specific protein, aquaporin-4 (AQP4).[5,12] 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.[3,13,14]

It most commonly affects women and begins in the mid-30s. Men and children may also develop NMOSD, but it is even more rare.[15,16] 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.[5-7,17,18] 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.[6-8] NMOSD is a distinct disease from other CNS diseases, including multiple sclerosis. The journey to diagnosis can be long, with the disease sometimes misdiagnosed.[19-21]

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.[22]

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® (ravulizumab-cwvz)

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, Japan and other countries for the treatment of certain adults with generalized myasthenia gravis (gMG).

ULTOMIRIS is also approved in the US, EU, Japan and other countries 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, Japan and other countries for certain adults and children with atypical hemolytic uremic syndrome to inhibit complement-mediated thrombotic microangiopathy (aHUS).

Further, ULTOMIRIS is approved in the US, 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 70 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 www.astrazeneca-us.com and follow the Company on social media @AstraZeneca.

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Dr. Pittock has provided consulting services to Alexion.