ULTOMIRIS™ (ravulizumab-cwvz)

For the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH)

ULTOMIRIS is the first and only long-acting medication approved by the FDA dosed every 8 weeks* to treat PNH in adults

*During maintenance phase.

INDICATION
What is ULTOMIRIS?
ULTOMIRIS is a prescription medicine called a monoclonal antibody. ULTOMIRIS is used to treat adults with a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH). It is not known if ULTOMIRIS is safe and effective 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. ULTOMIRIS can lower the ability of your immune system to fight infections.

- ULTOMIRIS increases your chance of getting serious and life-threatening meningococcal infections. Meningococcal infections 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 have not already had this vaccine.
2. If your doctor 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 before starting ULTOMIRIS. Your doctor will decide if you need additional meningococcal vaccination.
5. Meningococcal vaccines reduce the risk of meningococcal infection but do not prevent all meningococcal infections. Call your doctor 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 with a stiff neck or stiff back
   - fever and a rash
   - muscle aches with flu-like symptoms
   - headache and fever
   - fever
   - confusion
   - eyes sensitive to light

Please see Important Safety Information on pages 12-13. Please see the accompanying full Prescribing Information and Medication Guide for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.
Have you ever wondered if there might be another way to manage your PNH?

Great strides have been made in the treatment of PNH, but more still needs to be done. Are you ready for a change in the way you manage your PNH?

- Are frequent infusions a constant reminder that you are living with PNH?
- Are you planning your life around your infusion schedule?

ULTOMIRIS™ (ravulizumab-cwvz) is the first long-acting medication approved by the FDA dosed every 8 weeks to treat PNH.

ULTOMIRIS is a complement inhibitor indicated for the treatment of adult patients with PNH.

- With every-8-week dosing, ULTOMIRIS means your plans don't have to center around your infusions.

Understanding your treatment options may help minimize the impact PNH has on your daily life.

**ULTOMIRIS**

**INDICATION**

What is ULTOMIRIS?

ULTOMIRIS is a prescription medicine called a monoclonal antibody. ULTOMIRIS is used to treat adults with a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH). It is not known if ULTOMIRIS is safe and effective 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. ULTOMIRIS can lower the ability of your immune system to fight infections.

- ULTOMIRIS increases your chance of getting serious and life-threatening meningococcal infections.

Meningococcal infections may quickly become life-threatening and cause death if not recognized and treated early.  

1. You must receive meningococcal vaccine at least 2 weeks before your first dose of ULTOMIRIS if you have not already had this vaccine.
2. If your doctor 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 before starting ULTOMIRIS. Your doctor will decide if you need additional meningococcal vaccination.

5. Meningococcal vaccines reduce the risk of meningococcal infection but do not prevent all meningococcal infections. Call your doctor or get emergency medical care right away if you get one of these signs and symptoms of a meningococcal infection:
   - headache
   - stiff neck or stiff back
   - fever and a rash
   - muscle aches with flu-like symptoms
   - headache and fever
   - fever
   - confusion
   - eyes sensitive to light

Please see Important Safety Information on pages 12-13. Please see the accompanying full Prescribing Information and Medication Guide for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/epiglottis.
ULTOMIRIS™ (ravulizumab-cwvz) was designed to work in your body longer

ULTOMIRIS was shown to be effective for 8 weeks following maintenance dosing in clinical trials
• ULTOMIRIS starts working at the time of your first infusion and keeps working until it’s time for your next infusion
• ULTOMIRIS is dosed based on your weight

Switch with confidence
• ULTOMIRIS clinical studies involved more than 400 people who have been living with PNH
• In the largest PNH trial to date, ULTOMIRIS was studied in people starting treatment for the first time and those switching from eculizumab
• ULTOMIRIS demonstrated comparable efficacy to eculizumab in both clinical trials
• The most common side effects of ULTOMIRIS are upper respiratory infection and headache

In a clinical trial of people who had prior PNH treatment…

Nearly 9 of 10 people receiving ULTOMIRIS did not need a transfusion while receiving treatment

People taking ULTOMIRIS had no breakthrough events

At 6 months, 76% of both people taking ULTOMIRIS and people taking eculizumab had stable levels of hemoglobin

Breakthrough events are defined as experiencing at least 1 new or worsening sign or symptom of hemolysis that occurs along with elevated LDH levels (after LDH levels were previously reduced through treatment). Breakthrough events may lead to complications such as organ damage.

People taking ULTOMIRIS had levels of LDH (a marker that increases PNH activity) that stayed stable over time

Ask your doctor about the benefits of ULTOMIRIS

Ask your doctor about switching to ULTOMIRIS

Please see Important Safety Information on pages 12-13. Please see the accompanying full Prescribing Information and Medication Guide for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.
ULTOMIRIS™ (ravulizumab-cwvz) is a medicine that affects your immune system

ULTOMIRIS can lower the ability of your immune system to fight infections. ULTOMIRIS increases your chance of getting serious and life-threatening meningococcal infections. Meningococcal infections may quickly become life-threatening and cause death if not recognized and treated early.

You must receive meningococcal vaccines at least 2 weeks before your first dose of ULTOMIRIS unless you have already had this vaccine. If your doctor decides that urgent treatment with ULTOMIRIS is needed, you should receive meningococcal vaccination as soon as possible.

The importance of adhering to your prescribed treatment schedule

For ULTOMIRIS to reduce hemolysis, the drug needs to stay above a certain level in your blood. However, like all drugs, ULTOMIRIS is broken down and removed from your body over time.

The time that it takes your body to remove half of the drug is called the “half-life” of that drug. The half-life of ULTOMIRIS is about 50 days. A regular therapy schedule keeps ULTOMIRIS in your body at a level where it works best.

ULTOMIRIS should be infused according to the recommended dosing schedule for you to get the most out of your treatment. If the level of ULTOMIRIS in your body gets too low, hemolysis can occur. Hemolysis is the underlying cause of major health problems in PNH. Missing doses can cause hemolysis to happen. Work closely with your health care team to keep track of your infusions, and check in with your doctor regularly to best manage your PNH.

If you forget or miss an ULTOMIRIS infusion, call your doctor right away. To get the most from your ULTOMIRIS therapy, stick with your treatment schedule.

Infusion tips

You might be feeling unsure about getting intravenous infusions, but there are ways to improve the experience:

• Drink plenty of water. This will help your doctor find your veins more easily.
• Wear comfortable, layered clothing that you can adjust in case you become overly warm or cool.
• Keep busy during your infusion by reading, watching TV, or doing any other activity you can do while seated and remaining still.

You may need to arrive early or stay late after your treatment, depending on the requirements of your treatment center.

Lab values Things to keep in mind while on treatment

<table>
<thead>
<tr>
<th>Lab values</th>
<th>Things to keep in mind while on treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDH</td>
<td>• LDH is key for tracking the level of hemolysis caused by PNH</td>
</tr>
<tr>
<td></td>
<td>• It’s important to track over time to see how PNH is affecting you</td>
</tr>
<tr>
<td></td>
<td>• LDH levels, in comparison to your LDH level before starting ULTOMIRIS, show how well you are responding to ULTOMIRIS; the less LDH there is, the better ULTOMIRIS is working</td>
</tr>
<tr>
<td>Hemoglobin/anaemia</td>
<td>• In PNH, even if you don’t have anaemia, you might still be at risk for hemolysis and blood clots</td>
</tr>
<tr>
<td></td>
<td>• Hemoglobin is released into the bloodstream when red blood cells are destroyed by hemolysis</td>
</tr>
<tr>
<td></td>
<td>• When outside of cells, hemoglobin is harmful and is the cause of the signs, symptoms, and serious health problems associated with PNH</td>
</tr>
<tr>
<td></td>
<td>• Decreased hemoglobin levels during treatment do not ensure protection against hemolysis</td>
</tr>
<tr>
<td></td>
<td>• Hemoglobin levels in PNH patients with bone marrow problems might be low because of red blood cell production issues</td>
</tr>
<tr>
<td>Platelet counts</td>
<td>• Your platelet count might stay the same even after months of treatment, regardless of a decrease in LDH level and need for blood transfusions</td>
</tr>
<tr>
<td>Transfusion requirements</td>
<td>• Transfusions may still be necessary because ULTOMIRIS only treats hemolysis and not red blood cell production issues</td>
</tr>
</tbody>
</table>

TREATMENT CONSIDERATIONS

To manage PNH more effectively, learn all you can about the disease, work closely with your doctor, and take ULTOMIRIS according to your dosing schedule.
What do I need to know before taking ULTOMIRIS™ (ravulizumab-cwvz)?

How is ULTOMIRIS given?

For ULTOMIRIS to work properly, the way that it is given to you is important:
- ULTOMIRIS dosing is determined based on how much you weigh
- ULTOMIRIS is given as an infusion into a vein in your hand or arm
- The actual infusion usually takes just over 2 hours, but will vary based on body weight
- You will start with 2 infusions over a 2 week period
- Then you will receive an infusion every 8 weeks

Infusions must be given by trained health care professionals. After each infusion, you will be monitored for 1 hour for allergic reactions.

Switching to ULTOMIRIS from eculizumab:
- 2 weeks after your final eculizumab dose, your doctor will administer what’s known as a “loading dose” — this will only occur when you begin treatment with ULTOMIRIS
- 2 weeks after you receive the loading dose, you will receive your first “maintenance dose,” the dose at which you will continue to receive ULTOMIRIS once every 8 weeks

Allergic reactions

Serious allergic reactions can happen during your ULTOMIRIS infusion.
Tell your doctor or nurse right away if you get these symptoms during your ULTOMIRIS infusion: chest pain, trouble breathing or shortness of breath, swelling of your face, tongue, or throat, or if you feel faint or pass out.

If you have an allergic reaction during your ULTOMIRIS infusion, your doctor may need to infuse ULTOMIRIS more slowly, or stop ULTOMIRIS.

If you have an allergic reaction during your ULTOMIRIS infusion, your doctor or nurse will make sure you receive this vaccine at least 2 weeks before your first infusion.

Serious allergic reactions can happen during your ULTOMIRIS infusion. If your doctor decides that urgent treatment with ULTOMIRIS is needed, you should get the meningococcal vaccine as soon as possible.

If you had a meningococcal vaccine in the past, you might need additional vaccination before starting ULTOMIRIS. Your doctor will decide if you need additional meningococcal vaccination.

What should I know about the risk of infection?

Before your first infusion, talk to your doctor. Let your doctor know:
- If you have an infection or fever
- If you are pregnant, plan to become pregnant, or are nursing
- About the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements

You must receive meningococcal vaccines at least 2 weeks before your first dose of ULTOMIRIS if you have not already had this vaccine

Get vaccinated. ULTOMIRIS can lower the ability of your immune system to fight some infections. Before taking ULTOMIRIS, you must be vaccinated against meningococcal infection, a severe infection that can occur in the blood and that requires immediate medical attention.

Your doctor or nurse will make sure you receive this vaccine at least 2 weeks before your first infusion.

You should immediately call your doctor or seek emergency medical care, preferably in a major emergency medical care center:
- Fever
- Headache with a stiff neck or stiff back
- Headache and a fever
- Headache with nausea or vomiting
- Fever and a rash
- Confusion
- Muscle aches with flu-like symptoms
- Eyes sensitive to light

What are the symptoms of meningococcal infection?

The same mechanism that ULTOMIRIS uses to control hemolysis can increase your risk of getting an infection, especially a meningococcal infection.

Call your doctor or get emergency medical care right away if you get any of these signs or symptoms of a meningococcal infection:
- Fever
- Headache with a stiff neck or stiff back
- Headache and a fever
- Headache with nausea or vomiting
- Fever and a rash
- Confusion
- Muscle aches with flu-like symptoms
- Eyes sensitive to light

If you experience any of the following symptoms, you should immediately call your doctor or seek emergency medical care:
- Fever
- Headache with a stiff neck or stiff back
- Headache and a fever
- Headache with nausea or vomiting
- Fever and a rash
- Confusion
- Muscle aches with flu-like symptoms
- Eyes sensitive to light

Get vaccinated.

If you have not already had this vaccine, you should get the meningococcal vaccine as soon as possible.

If your doctor decides that urgent treatment with ULTOMIRIS is needed, you should get the meningococcal vaccine as soon as possible.

If you had a meningococcal vaccine in the past, you might need additional vaccination before starting ULTOMIRIS. Your doctor will decide if you need additional meningococcal vaccination.

If you had a meningococcal vaccine in the past, you might need additional vaccination before starting ULTOMIRIS. Your doctor will decide if you need additional meningococcal vaccination.

If you had a meningococcal vaccine in the past, you might need additional vaccination before starting ULTOMIRIS. Your doctor will decide if you need additional meningococcal vaccination.

Start carrying your ULTOMIRIS Patient Safety Information Card when you begin receiving treatment.

Similar to when you started eculizumab, your doctor will give you a Patient Safety Information Card about the risk of meningococcal infection when you start taking ULTOMIRIS. You can find a Patient Safety Information Card in the back of this brochure that lists the signs and symptoms of a meningococcal infection and tells you what to do if you experience any of them.

Show this card to any health care professional involved in treating you for any issues, whether or not they are related to PNH.

Please see Important Safety Information on pages 12-13. Please see the accompanying full Prescribing Information and Medication Guide for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/epiglottis.
Connect with resources for people living with PNH

Available at no cost to people living with PNH, you can get one-on-one support from an Alexion Nurse Case Manager. OneSource™ can help you learn about PNH, co-verify your insurance coverage, and identify helpful resources for people living with PNH and those who care for them. And through the Buddy Program, an Alexion Nurse Case Manager can put you in touch with other people just like you who are living with PNH. All you have to do is ask.

OneSource is here to help

You and your physician can call the complimentary OneSource Patient Support Program and speak with a dedicated Alexion Nurse Case Manager who has advanced education in PNH, health insurance expertise, and information on funding and community resources.

PNH Resources

Where can I find out more?

It is natural to think you are alone when you are diagnosed with PNH, because it is an ultra-rare disease. Communicating with others who have had similar experiences and who understand can make a difference. Here are some organizations that offer information and support:

• The Aplastic Anemia and MDS International Foundation (AAMDSIF): supports, connects, and educates patients, caregivers, and health professionals on bone marrow failure diseases worldwide. It promotes and invests in collaborative clinical research to accelerate the discovery of better treatments and cures for aplastic anemia, myelodysplastic syndrome (MDS), PNH, and related bone marrow failure diseases

• National Institutes of Health (NIH): part of the US Department of Health and Human Services and a trusted source of research

• National Organization for Rare Disorders (NORD): a not-for-profit organization dedicated to helping people with rare disorders such as PNH

To learn more visit ULTOMIRIS.com
ULTOMIRIS is a prescription medicine called a monoclonal antibody. ULTOMIRIS is used to treat adults with a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH). It is not known if ULTOMIRIS is safe and effective in children.

IMPORTANT SAFETY INFORMATION

What is the most important information I should know before taking ULTOMIRIS?

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

• ULTOMIRIS increases your chance of getting serious and life-threatening meningococcal infections. Meningococcal infections 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 have not already had this vaccine.

2. Your doctor 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 receive 2 weeks of antibiotics with your vaccinations.

4. If you had a meningococcal vaccine in the past, you might need additional vaccinations before starting ULTOMIRIS. Your doctor will decide if you need additional meningococcal vaccination.

5. Meningococcal vaccines reduce the risk of meningococcal infection but do not prevent all meningococcal infections. Call your doctor or get emergency medical care right away if you get any of these symptoms and a meningococcal infection is needed, you should receive meningococcal vaccination as soon as possible.

• Headache with nausea or vomiting
• Headache with a stiff neck or stiff back
• Fever and a rash
• Muscle aches with flu-like symptoms
• Headache and fever
• Fever
• Cough
• Eyes sensitive to light

Your doctor 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. 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 doctor or nurse who treats you. This will help them diagnose and treat you quickly.

ULTOMIRIS is only available through a program called the ULTOMIRIS REMS. Before you can receive ULTOMIRIS, your doctor must:

• enroll in the ULTOMIRIS REMS program
• counsel you about the risk of meningococcal infection
• give you information about the symptoms of meningococcal infection

• give you a Patient Safety Card about your risk of meningococcal infection, as discussed above
• make sure that you are vaccinated with a meningococcal vaccine

ULTOMIRIS may also increase the risk of other types of serious infections.

• People who take ULTOMIRIS may have an increased risk of getting infections caused by Streptococcus pneumoniae and Haemophilus influenzae.

• Certain people may also have an increased risk of gonorrhea infection. Talk to your healthcare provider to find out if you are at risk for gonorrhea infection, about gonorrhea prevention, and regular testing.

Call your healthcare provider right away if you have any new signs or symptoms of infection.

Who should not receive ULTOMIRIS?

Do not start ULTOMIRIS if you have a meningococcal infection. Before you receive ULTOMIRIS, tell your doctor about all of your medical conditions, including if you:

• have an infection or fever
• are pregnant or plan to become pregnant. It is not known if ULTOMIRIS will harm your unborn baby.
• are breastfeeding or plan to breastfeed. It is not known if ULTOMIRIS passes into your breast milk. You should not breastfeed during treatment and for 8 months after your final dose of ULTOMIRIS.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ULTOMIRIS and other medicines can affect each other causing side effects.

Know the medications you take and you vaccine you receive. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I receive ULTOMIRIS?

• ULTOMIRIS is given through a vein by intravenous (I.V.) infusion usually over about 2 hours.

• You will usually receive:
  • a starting dose of ULTOMIRIS as an infusion by your doctor, and then
  • 2 weeks later, you will start to receive an infusion of ULTOMIRIS every 8 weeks.

• If you are changing treatment from SOLIRIS to ULTOMIRIS, you should receive a starting dose of ULTOMIRIS 2 weeks after your last dose of SOLIRIS.

• After such infection, you should take a course of at least 1 hour for allergic reactions. See “What are the possible side effects of ULTOMIRIS?”

• If you stop receiving ULTOMIRIS, your doctor 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.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ULTOMIRIS and other medicines can affect each other causing side effects.

Know the medications you take and you vaccine you receive. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

• 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 Brand WARNING regarding serious and life-threatening meningococcal infections/appear.

Symptoms or problems that can happen due to red blood cell breakdown include:

• drop in the number of your red blood cells count
• weakness, tiredness
• swelling of your face, tongue, or throat
• shortness of breath

Tell your doctor if these symptoms bother you or that do not go away. These are not all the possible side effects of ULTOMIRIS. For more information, ask your doctor or pharmacist.

Call your doctor 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 Brand WARNING regarding serious and life-threatening meningococcal infections/appear.
Anemia: The condition of having a lower-than-normal number of red blood cells or amount of hemoglobin. Anemia reduces the ability of the blood to carry oxygen and is sometimes found in PNH.

Blood clots: Blood clots form when parts of your body’s blood clump together. In a healthy body, this clumping can stop bleeding when you’re cut or injured, but in certain conditions, these clumps can block blood flow in the veins and arteries, which can be dangerous. In PNH, a clot can happen at any time and can cause serious health problems.

Breakthrough events: Breakthrough events, or breakthrough hemolysis, are defined as at least 1 new or worsening symptom of hemolysis that occurs along with elevated LDH levels (after LDH levels were previously reduced to normal levels). Breakthrough events may lead to complications such as organ damage.

Complement: Part of the complement cascade. In healthy individuals, it is a sequence of protein reactions in the blood that is part of the body’s natural defense system. It helps fight against bacteria and other foreign matter in the body.

Hemolysis: When red blood cells break down. Hemolysis is the main cause of major health problems in PNH.

Kidney damage: Healthy kidneys clean your blood by removing excess fluid, minerals, and wastes. They also make hormones that keep your bones strong and your blood healthy. In PNH, the blood clots that burst release iron and hemoglobin into your system. As a result, blood vessels in the kidneys can get injured. This injury reduces the level at which your kidneys work.

Paroxysmal nocturnal hemoglobinuria (PNH): A disease where red blood cells are created without certain protective proteins. This causes them to break down (a process called hemolysis) and can result in serious health problems. Signs and symptoms include stomach pain, difficulty swallowing, anemia, shortness of breath, and fatigue. Life-threatening complications from PNH include blood clots, which may lead to kidney failure and damage to your other organs.

Proteins: Proteins are the building blocks of life. The body needs proteins to repair and maintain itself. In PNH, some or all red blood cells lack an important protective protein. Without this protein, PNH red blood cells are attacked by complement, part of the body’s natural defense system, resulting in hemolysis.

Red blood cells (RBCs): A type of cell found in your blood that delivers oxygen and removes waste (carbon dioxide) in your body. Red blood cells affected by PNH are attacked and destroyed because they are missing a protective protein.
Have you ever wondered if there might be another way to treat your PNH?

ULTOMIRIS™ (ravulizumab-cwvz) was shown to be effective for 8 weeks following maintenance dosing in clinical trials

- ULTOMIRIS starts working at the time of your first infusion and keeps working until it's time for your next infusion
- With every-8-week dosing, ULTOMIRIS means your plans don't have to center around your infusions
- ULTOMIRIS clinical studies involved more than 400 people who have been living with PNH
- In the largest PNH trial to date, ULTOMIRIS was studied in people starting treatment for the first time and those switching from eculizumab
- ULTOMIRIS demonstrated comparable efficacy to eculizumab in both clinical trials

You and your physician can call the complimentary OneSource™ Patient Support Program and speak with a dedicated Alexion Nurse Case Manager who has advanced education in PNH, health insurance expertise, and information on funding and community resources.

Call 1-888-765-4747, email OneSource@Alexion.com or visit www.AlexionOneSource.com

INDICATION
What is ULTOMIRIS?

ULTOMIRIS is a prescription medicine called a monoclonal antibody.
ULTOMIRIS is used to treat adults with a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH). It is not known if ULTOMIRIS is safe and effective 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.
ULTOMIRIS can lower the ability of your immune system to fight infections.
- ULTOMIRIS increases your chance of getting serious and life-threatening meningococcal infections. Meningococcal infections 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 have not already had this vaccine.
2. If your doctor 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 before starting ULTOMIRIS. Your doctor will decide if you need additional meningococcal vaccination.
5. Meningococcal vaccines reduce the risk of meningococcal infection but do not prevent all meningococcal infections. Call your doctor 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 with a stiff neck or stiff back
   - fever and a rash
   - muscle aches with flu-like symptoms
   - headache and fever
   - fever
   - confusion
   - eyes sensitive to light

Please see Important Safety Information on pages 12-13. Please see the accompanying full Prescribing Information and Medication Guide for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.
ULTOMIRIS™ (ravulizumab-cwvz) injection, for intravenous use

**INDICATIONS AND USAGE**
ULTOMIRIS is a complement inhibitor indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

**DOSAGE FORMS AND STRENGTHS**
ULTOMIRIS™ (ravulizumab-cwvz) injection, for intravenous use is available as a single-dose vial in two strengths:
- 300 mg/30 mL (10 mg/mL) in a single-dose vial (3).
- 300 mg/30 mL (10 mg/mL) in a single-dose vial (3).

**CONTRAINdications**
ULTOMIRIS is contraindicated in patients with unresolved Neisseria Meningitidis infection (4).

**ADVERSE REACTIONS**
The most frequent adverse drug reactions (>10%) were upper respiratory infection and headache (6.1).

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.

See 17 PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2018

<table>
<thead>
<tr>
<th>Body Weight Range (kg)</th>
<th>Loading Dose (mg)</th>
<th>Maintenance Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than or equal to 40 to less than 60</td>
<td>2,400</td>
<td>3,000</td>
</tr>
<tr>
<td>greater than or equal to 60 to less than 100</td>
<td>2,700</td>
<td>3,300</td>
</tr>
<tr>
<td>greater than or equal to 100</td>
<td>3,000</td>
<td>3,600</td>
</tr>
</tbody>
</table>

See Full Prescribing Information for important preparation and administration instructions (2.2, 2.3).

**PRECAUTIONS**

**5.1 Serious Meningococcal Infections**

Vaccination reduces, but does not eliminate, the risk of meningococcal infections.

- Vaccination may be considered for patients who are either at higher risk or who have increased exposure to meningococcal infections.
- Do not vaccinate if the patient is suspected of having a meningococcal infection.

**5.2 Other Infections**

Use caution when administering ULTOMIRIS to patients with any other systemic infection.

**5.3 Monitoring Disease Manifestations after ULTOMIRIS Discontinuation**

**5.4 Thromboembolic Event Management**

**5.5 Infusion Reactions**

**6 ADVERSE REACTIONS**

**6.1 Clinical Trial Experience**

**6.2 Immunogenicity**

**DOSAGE AND ADMINISTRATION**

Only administer as an intravenous infusion.

**2.3 Preparation and Administration**

Provide 2 weeks of antibacterial drug prophylaxis to patients if ULTOMIRIS must be initiated immediately and infection is suspected.

**2.2 Recommended Weight-Based Dosage Regimen**

The recommended dosing regimen for adult patients (>18 years of age) with PNH consists of a loading dose followed by maintenance dosing, administered by intravenous infusion. Administer the doses based on the patient's body weight, as shown in Table 1. Starting 2 weeks after the loading dose administration, begin maintenance doses at a once every 8-week interval. The dosing schedule is allowed to occasionally vary within 7 days of the scheduled infusion day (except for the first maintenance dose of ULTOMIRIS) but the subsequent dose should be administered according to the original schedule.

For patients switching from eculizumab to ULTOMIRIS, administer the loading dose of ULTOMIRIS 2 weeks after the last eculizumab infusion, and then administer maintenance doses once every 8 weeks, starting 2 weeks after loading dose administration, as shown in Table 1.

**14.1 Study in Complement-Inhibitor Naive Patients with PNH**

**14.2 Study in Eculizumab-Experienced Patients with PNH**

**17 PATIENT COUNSELING INFORMATION**

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

**8.2 Lactation**

**8.4 Pediatric Use**

**8.5 Geriatric Use**

**9 CLINICAL PHARMACOLOGY**

**11 DESCRIPTION**

**12 CLINICAL PHARMACOLOGY**

**13 NONCLINICAL TOXICOLOGY**

**14 CLINICAL STUDIES**

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**17 PATIENT COUNSELING INFORMATION**

*Sections or subsections omitted from the full prescribing information are not listed*
Enrollment in the ULTOMIRIS REMS and additional information are available by telephone: 1-888-765-4747 or at the REMS educational materials, and ensure patients are vaccinated with meningococcal vaccines.

Due to the risk of meningococcal infections, ULTOMIRIS is available only through a restricted program under REMS. No prophylaxis is required. Meningococcal disease due to any serogroup may occur. Vaccination reduces, but does not eliminate, the risk of meningococcal infections. In clinical studies, 3 out of 222 patients with PNH treated with ULTOMIRIS experienced inflection reactions (lower back pain, drop in blood pressure and infusion-related pain) during ULTOMIRIS administration. 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 ADVERSE REACTIONS
The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Serious Meningococcal Infections [see Warnings and Precautions (5.1)].
- Other Infections [see Warnings and Precautions (5.2)].
- Monitoring PNH Disease Manifestations after ULTOMIRIS Discontinuation [see Warnings and Precautions (5.3)].
- Infusion Reactions [see Warnings and Precautions (5.5)].

6.1 Clinical Trial Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure of 441 adult patients with PNH in Phase 3 studies who received ULTOMIRIS (n = 222) or eculizumab (n = 219) at the recommended dosing regimens with median treatment duration of 6 months for ULTOMIRIS and 6 months for eculizumab. The most frequent types of drug reactions (>10%) with ULTOMIRIS were upper respiratory tract infection and headache. Table 4 describes adverse reactions that occurred at a rate of 5% or more among patients treated with ULTOMIRIS. Serious adverse reactions were reported in 15 (6.8%) patients receiving ULTOMIRIS. The serious adverse reactions in patients treated with ULTOMIRIS included hyperthermia and pyrexia. No serious adverse reaction was reported in more than 1 patient treated with ULTOMIRIS.

One fatal case of sepsis was identified in a patient treated with ULTOMIRIS.

Table 4: Adverse Reactions Reported In 5% or More of ULTOMIRIS Treated Patients in Complement Inhibitor Naive and Eculizumab-Experienced Patients with PNH

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>ULTOMIRIS (n=222)</th>
<th>Eculizumab (n=219)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19 (9)</td>
<td>12 (5)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>19 (9)</td>
<td>19 (9)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13 (6)</td>
<td>16 (7)</td>
<td></td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>15 (7)</td>
<td>18 (8)</td>
<td></td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infectiona</td>
<td>86 (39)</td>
<td>86 (39)</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>14 (6)</td>
<td>11 (5)</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11 (5)</td>
<td>12 (5)</td>
<td></td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>71 (32)</td>
<td>57 (26)</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>12 (5)</td>
<td>14 (6)</td>
<td></td>
</tr>
<tr>
<td>a Grouped term included: Nasopharyngitis, Upper respiratory tract infection, Oropharyngeal pain, Viral upper respiratory tract infection, Rhinitis, Respiratory tract infection, Rhinorrhea, Pharyngitis, and Upper respiratory tract infiammation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6.2 Immunogenicity
As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the specificity and sensitivity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibodies) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other studies or to other studies may be misleading.

The immunogenicity of ravulizumab-cwvz has been evaluated using an enzyme linked immunosorbent assay (ELISA) for the detection of binding anti-ravulizumab-cwvz antibodies. For patients whose sera tested positive in the screening immunoassay, an in vitro biological assay was performed to detect neutralizing antibodies.

In clinical studies of patients with PNH, treatment-emergent antibodies to ravulizumab-cwvz were detected in 1 of 209 (0.5%) patients. No apparent correlation of antibody development to altered pharmacokinetic profile, clinical response, or adverse events was observed.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no available data on ULTOMIRIS use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with untreated parovascular neonatal hemoglobinuria (PNH) in pregnancy (see Clinical Considerations). Animal studies using a mouse analogue of the ravulizumab-cwvz molecule (murine anti-C5 antibody) showed increased rates of developmental abnormalities and an increased rate of dead and m bannering offspring at doses 0.5 2.2 times the human dose (see Data).

Table 2: Loading Dose Administration Reference Table

<table>
<thead>
<tr>
<th>Body Weight Range (kg)*</th>
<th>Loading Dose (mg)</th>
<th>ULTOMIRIS Volume (mL)</th>
<th>Volume of NaCl Diluent® (mL)</th>
<th>Total Volume (mL)</th>
<th>Maximum Infusion Rate (mL/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than or equal to 40 to less than 60</td>
<td>2,400</td>
<td>240</td>
<td>240</td>
<td>480</td>
<td>252</td>
</tr>
<tr>
<td>greater than or equal to 60 to less than 100</td>
<td>2,700</td>
<td>270</td>
<td>270</td>
<td>540</td>
<td>317</td>
</tr>
<tr>
<td>greater than or equal to 100</td>
<td>3,000</td>
<td>300</td>
<td>300</td>
<td>600</td>
<td>333</td>
</tr>
</tbody>
</table>

*Body weight at time of treatment

Table 3: Maintenance Dose Administration Reference Table

<table>
<thead>
<tr>
<th>Body Weight Range (kg)*</th>
<th>Maintenance Dose (mg)</th>
<th>ULTOMIRIS Volume (mL)</th>
<th>Volume of NaCl Diluent® (mL)</th>
<th>Total Volume (mL)</th>
<th>Maximum Infusion Rate (mL/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than or equal to 40 to less than 60</td>
<td>3,000</td>
<td>300</td>
<td>300</td>
<td>600</td>
<td>257</td>
</tr>
<tr>
<td>greater than or equal to 60 to less than 100</td>
<td>3,300</td>
<td>330</td>
<td>330</td>
<td>660</td>
<td>330</td>
</tr>
<tr>
<td>greater than or equal to 100</td>
<td>3,600</td>
<td>360</td>
<td>360</td>
<td>720</td>
<td>327</td>
</tr>
</tbody>
</table>

*Body weight at time of treatment

a Dilute ULTOMIRIS only using 0.9% Sodium Chloride Injection, USP.

Prior to administration, allow the admixture to adjust to room temperature (18°-25°C, 64°-77°F). Do not heat the admixture in a microwave or with any heat source other than ambient air temperature. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

If an adverse reaction occurs during the administration of ULTOMIRIS, the infusion may be slowed or stopped at the discretion of the physician. Monitor the patient for at least one hour following completion of the infusion for signs or symptoms of an infusion reaction.

3 DOSAGE FORMS AND STRENGTHS
Injection: 300 mg/30 mL (10 mg/mL) as a clear to translucent, slight whitish color solution in a single-dose vial.

4 CONTRAINDICATIONS
ULTOMIRIS is contraindicated in patients with unresolved Neisseria meningitidis infection [see Warnings and Precautions (5.1)].

5 WARNINGS AND PRECAUTIONS
5.1 Serious Meningococcal Infections
Risk and Prevening
Life-threatening meningococcal infections have occurred in patients treated with ULTOMIRIS. The use of ULTOMIRIS increases a patient’s susceptibility to serious meningococcal infections (septicaemia and/or meningitis). Meningococcal disease due to any serogroup may occur.

Vaccinate for meningococcal disease according to the most current Advisory Committee on Immunization Practices (ACIP) recommendations for patients with complement deficiencies. Revaccinate patients in accordance with ACIP recommendations considering the duration of ULTOMIRIS therapy.

Immunize patients without a history of meningococcal vaccination at least 2 weeks prior to receiving the first dose of ULTOMIRIS. If urgent ULTOMIRIS therapy is indicated in an unvaccinated patient, administer meningococcal vaccine(s) as soon as possible and provide patients with 2 weeks of antibacterial drug prophylaxis.

In clinical studies, 59 patients with PNH were treated with ULTOMIRIS less than 2 weeks after meningococcal vaccination. All of these patients received antibiotics for prophylaxis of meningococcal infection until at least 2 weeks after meningococcal vaccination. The benefits and risks of antibiotic prophylaxis for prevention of meningococcal infections in patients receiving ULTOMIRIS have not been established.

Vaccination reduces, but does not eliminate, the risk of meningococcal infections. In clinical studies, 3 out of 261 PNH patients developed serious meningococcal infections/sepsis while receiving treatment with ULTOMIRIS; all 3 had been vaccinated. These 3 patients recovered while continuing treatment with ULTOMIRIS.

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 acts to be taken to seek immediate medical care. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early. Consider discontinuation of ULTOMIRIS in patients who are undergoing treatment for serious meningococcal infection.

REMS
Due to the risk of meningococcal infections, ULTOMIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the ULTOMIRIS REMS, prescribers must enroll in the program.

Prescribers must counsel patients about the risk of meningococcal infection/sepsis, provide the patients with the REMS educational materials, and ensure patients are vaccinated with meningococcal vaccines.

Enrollment in the ULTOMIRIS REMS and additional information are available by telephone: 1-888-765-4747 or at www.ultomirisrems.com.
Complement n (%)
17 (13.6)

Previously Treated with
95
1386 ± 268 (19.4)
17 (13.6)
22 (18.2)
22 (17.6)
1379 ± 276 (20.0)
771 ± 166 (21.5)
96
25 (20.7)
Mean (SD)
ULTOMIRIS
LD = Loading Dose; MD = Maintenance Dose

Table 5: Mean ± SD (%CV) Pharmacokinetic Parameters of ULTOMIRIS in Patients with PNH who are Complement Inhibitor-Naïve or Previously Treated with Eculizumab

Table 6: Baseline Characteristics in the Complement-Inhibitor Naïve Study

Parameter
Statistics
ULTOMIRIS (N = 125)
Eculizumab (N = 121)
Age (years) at first infusion in study
Mean (SD), Min, max
44.5 (12.5), 18, 83
46.2 (16.2), 18, 86
Sex
Male
65 (52.0)
69 (57.0)
Race
Asian
72 (57.6)
57 (47.1)
White
43 (34.4)
51 (42.1)
Black or African American
2 (1.6)
4 (3.3)
American Indian or Alaska Native
1 (0.8)
1 (0.8)
Other
4 (3.2)
4 (3.3)
Not reported
3 (2.4)
3 (4.3)
Pre-treatment LDH levels (U/L)
Median (Min, max)
1513.5 (378.0, 3759.5)
1445.0 (423.5, 3139.5)
Units of PRBC/whole blood transfused within 12 months prior to first dose
Median (Min, max)
6.0 (1.14)
6.0 (1.32)
Antithrombotic agents used within 28 days prior to first dose
n (%)
22 (17.6)
22 (18.2)
Patients with a history of MAVEa
n (%)
17 (13.6)
25 (20.7)
Patients with a history of thrombosis
n (%)
17 (13.6)
20 (16.5)
Patients with concomitant anticoagulant treatment
n (%)
23 (18.4)
28 (23.1)

Table: Baseline Characteristics in the Complement-Inhibitor Naïve Study

Table 5: Mean ± SD (%CV) Pharmacokinetic Parameters of ULTOMIRIS in Patients with PNH who are Complement Inhibitor-Naïve or Previously Treated with Eculizumab

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Statistics</th>
<th>ULTOMIRIS (N = 125)</th>
<th>Eculizumab (N = 121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) at first infusion in study</td>
<td>Mean (SD), Min, max</td>
<td>44.5 (12.5), 18, 83</td>
<td>46.2 (16.2), 18, 86</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>n (%)</td>
<td>65 (52.0)</td>
<td>69 (57.0)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>n (%)</td>
<td>72 (57.6)</td>
<td>57 (47.1)</td>
</tr>
<tr>
<td>White</td>
<td></td>
<td>43 (34.4)</td>
<td>51 (42.1)</td>
</tr>
<tr>
<td>Black or African American</td>
<td></td>
<td>2 (1.6)</td>
<td>4 (3.3)</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td></td>
<td>1 (0.8)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>4 (3.2)</td>
<td>4 (3.3)</td>
</tr>
<tr>
<td>Not reported</td>
<td></td>
<td>3 (2.4)</td>
<td>3 (4.3)</td>
</tr>
<tr>
<td>Pre-treatment LDH levels (U/L)</td>
<td>Median (Min, max)</td>
<td>1513.5 (378.0, 3759.5)</td>
<td>1445.0 (423.5, 3139.5)</td>
</tr>
<tr>
<td>Units of PRBC/whole blood transfused within 12 months prior to first dose</td>
<td>Median (Min, max)</td>
<td>6.0 (1.14)</td>
<td>6.0 (1.32)</td>
</tr>
<tr>
<td>Antithrombotic agents used within 28 days prior to first dose</td>
<td>n (%)</td>
<td>22 (17.6)</td>
<td>22 (18.2)</td>
</tr>
<tr>
<td>Patients with a history of MAVEa</td>
<td>n (%)</td>
<td>17 (13.6)</td>
<td>25 (20.7)</td>
</tr>
<tr>
<td>Patients with a history of thrombosis</td>
<td>n (%)</td>
<td>17 (13.6)</td>
<td>20 (16.5)</td>
</tr>
<tr>
<td>Patients with concomitant anticoagulant treatment</td>
<td>n (%)</td>
<td>23 (18.4)</td>
<td>28 (23.1)</td>
</tr>
</tbody>
</table>

a *Other* as specified on case report form included thrombocytopenia, chronic kidney disease, and pancytopenia, as well as a number of other conditions.

MAVE = major adverse vascular event

Efficacy was established based upon transfusion avoidance and hemolysis as directly measured by normalization of LDH levels. Transfusion avoidance was defined as patients who did not receive a transfusion and not meet the protocol specified guidelines for transfusion from baseline up to Day 183. Supportive efficacy data included the percent change from baseline in LDH levels, the proportion of patients with breakthrough hemolysis defined as at least one new or worsening symptom or sign of intravascular hemolysis in the presence of elevated LDH ≥ 2 × ULN, after prior LDH reduction to < 1.5 × ULN on therapy and the proportion of patients with stabilized hemoglobin.
Non-inferiority of ULTOMIRIS to eculizumab was demonstrated across endpoints in the complement inhibitor naïve treatment population described in the table below.

Table 7: Efficacy Results in the Complement-Inhibitor naïve Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ULTOMIRIS (N=125)</th>
<th>Eculizumab (N=121)</th>
<th>Statistic for Comparison</th>
<th>Treatment Effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion avoidance rate</td>
<td>0.62%</td>
<td>0.70%</td>
<td>Difference in rate</td>
<td>0.9 (-0.8, 2.4)</td>
</tr>
<tr>
<td>LDH normalization</td>
<td>5.6%</td>
<td>5.0%</td>
<td>Odds ratio</td>
<td>0.9 (0.5, 1.6)</td>
</tr>
<tr>
<td>LDH percent change</td>
<td>-7.6%</td>
<td>-7.0%</td>
<td>Difference in % change</td>
<td>-0.6 (-5.2, 3.0)</td>
</tr>
<tr>
<td>Breakthrough hemolysis</td>
<td>4.0%</td>
<td>10.7%</td>
<td>Difference in rate</td>
<td>6.8 (-14.2, 0.4)</td>
</tr>
<tr>
<td>Hemoglobin stabilization</td>
<td>68.8%</td>
<td>65.4%</td>
<td>Difference in rate</td>
<td>2.9 (-8.0, 14.6)</td>
</tr>
</tbody>
</table>

Note: LDH = lactate dehydrogenase; CI = confidence interval

For the transfusion avoidance endpoint, treatment differences (95% CIs) are based on estimated differences in percent with 95% CI. For the lactate dehydrogenase normalization endpoint, the adjusted prevalence within each treatment is displayed.

There was no observable difference in fatigue between ULTOMIRIS and eculizumab after 26 weeks of treatment compared to baseline as measured by the FACT-fatigue instrument. Patient-reported fatigue may be an under- or over-estimation, because patients were not blinded to treatment assignment.

14.2 Study in Eculizumab-Experienced Patients with PNH

The study in eculizumab-experienced patients [ALXN1210-PNH-302; NCT03056040] was a 26-week, multicenter, open-label, randomized, active-controlled, non-inferiority Phase 3 study conducted in 195 patients with PNH who were clinically stable after having been treated with eculizumab for at least the past 6 months. Patients who demonstrated clinically stable disease after being treated with eculizumab for at least the prior 6 months were randomized 1:1 to either continue eculizumab or to switch to ULTOMIRIS. The mean total PNH granulocyte clone size was 83%, the mean total PNH monocyte clone size was 86%, and the mean total PNH RBC clone size was 60%. Ninety five percent of patients had a documented PNH-associated condition diagnosed prior to enrollment on the trial: anemia (67%), hematuria or hemoglobinuria (49%), history of aplastic anemia (37%), history of renal failure (9%), myelodysplastic syndrome (5%), pregnancy complication (7%), and other (14%). Major baseline characteristics were balanced between the two treatment groups.

Table 8: Baseline Characteristics in Eculizumab-Experienced Patients with PNH

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ULTOMIRIS (N = 97)</th>
<th>Eculizumab (N = 98)</th>
<th>Statistic for Comparison</th>
<th>Treatment Effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) at first infusion in study</td>
<td>Mean (SD) Min, max</td>
<td>46.6 (14.4) 18, 79</td>
<td>48.8 (13.9) 23, 77</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>n (%)</td>
<td>50 (51.5) 23 (23.7)</td>
<td>61 (62.2) 19 (19.4)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>50 (51.5) 23 (23.7)</td>
<td>61 (62.2) 19 (19.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>5 (5.2)</td>
<td>3 (3.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>2 (2.1)</td>
<td>1 (1.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (2.1)</td>
<td>1 (1.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not reported</td>
<td>13 (13.4)</td>
<td>13 (13.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (3.1)</td>
<td>1 (1.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple</td>
<td>1 (1.0)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>n (%)</td>
<td>50 (51.5) 23 (23.7)</td>
<td>48 (49.0) 23 (23.4)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>50 (51.5) 23 (23.7)</td>
<td>48 (49.0) 23 (23.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-treatment LDH levels (U/L)</td>
<td>Median Min, max</td>
<td>224.0</td>
<td>234.0</td>
<td></td>
</tr>
<tr>
<td>Units of PBC/whole blood transfused within 12 months prior to first dose</td>
<td>Median Min, max</td>
<td>135.0, 383.5</td>
<td>100.0, 365.5</td>
<td></td>
</tr>
<tr>
<td>Antithrombotic agents used within 28 days prior to first dose</td>
<td>n (%)</td>
<td>20 (20.6)</td>
<td>13 (13.3)</td>
<td></td>
</tr>
<tr>
<td>Patients with a history of MAVE</td>
<td>n (%)</td>
<td>28 (28.9)</td>
<td>22 (22.4)</td>
<td></td>
</tr>
<tr>
<td>Patients with a history of thrombosis</td>
<td>n (%)</td>
<td>27 (27.8)</td>
<td>21 (21.4)</td>
<td></td>
</tr>
<tr>
<td>Patients with concomitant anticoagulant treatment</td>
<td>n (%)</td>
<td>22 (22.7)</td>
<td>16 (16.3)</td>
<td></td>
</tr>
</tbody>
</table>

*MAVE = major adverse vascular event

Efficacy was established based on hemolysis as measured by LDH percent change from baseline to Day 183 and supportive efficacy data was transfusion avoidance, proportion of patients with stabilized hemoglobin, and the proportion of patients with breakthrough hemolysis through Day 183.

Non-inferiority of ULTOMIRIS to eculizumab was demonstrated across endpoints in the patients with PNH previously treated with eculizumab described in the table below.

Table 9: Efficacy Results in the Eculizumab-Experienced Patients with PNH Eculizumab-Experienced Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ULTOMIRIS (n = 97)</th>
<th>Eculizumab (n = 98)</th>
<th>Statistic for Comparison</th>
<th>Treatment Effect (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDH Percent change</td>
<td>-0.82%</td>
<td>0.4%</td>
<td>Difference in % change</td>
<td>9.2 (-4.2, 18.8)</td>
</tr>
<tr>
<td>Breakthrough hemolysis</td>
<td>0%</td>
<td>5.1%</td>
<td>Difference in % change</td>
<td>5.1 (-8.9, 19.0)</td>
</tr>
<tr>
<td>Transfusion avoidance</td>
<td>87.6%</td>
<td>82.7%</td>
<td>Difference in % change</td>
<td>5.5 (-4.3, 15.7)</td>
</tr>
<tr>
<td>Hemoglobin Stabilization</td>
<td>76.3%</td>
<td>75.5%</td>
<td>Difference in % change</td>
<td>4.4 (-10.4, 13.3)</td>
</tr>
</tbody>
</table>

Note: CI = confidence interval

There was no observable difference in fatigue between ULTOMIRIS and eculizumab after 26 weeks of treatment compared to baseline as measured by the FACT-fatigue instrument. Patient-reported fatigue may be an under- or over-estimation, because patients were not blinded to treatment assignment.
What is the most important information I should know about ULTOMIRIS?

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

- ULTOMIRIS increases your chance of getting serious and life-threatening meningococcal infections. Meningococcal infections 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 have not already had this vaccine.
2. If your doctor 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 before starting ULTOMIRIS. Your doctor will decide if you need additional meningococcal vaccination.
5. Meningococcal vaccines reduce the risk of meningococcal infection but do not prevent all meningococcal infections. Call your doctor 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 with a stiff neck or stiff back
   - fever
   - a rash
   - muscle aches with flu-like symptoms
   - eyes sensitive to light

Your doctor 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 final dose of ULTOMIRIS. It is important to show this card to any doctor or nurse who treats you. This will help them diagnose and treat you quickly.

ULTOMIRIS is only available through a program called the ULTOMIRIS REMS. Before you can receive ULTOMIRIS, your doctor must:
- enroll in the ULTOMIRIS REMS program
- counsel you about the risk of meningococcal infection
- give you information about the symptoms of meningococcal infection
- give you a Patient Safety Card about your risk of meningococcal infection, as discussed above
- make sure that you are vaccinated with a meningococcal vaccine

Ulottinrias may also increase the risk of other types of serious infections.
- People who take ULTOMIRIS may have an increased risk of getting infections caused by Streptococcus pneumoniae and Haemophilus influenzae.
- Certain people may also have an increased risk of gonorrhea infection. Talk to your healthcare provider to find out if you are at risk for gonorrhea infection, about gonorrhea prevention, and regular testing.

Call your healthcare provider right away if you have any new signs or symptoms of infection.

What is ULTOMIRIS?
ULTOMIRIS is a prescription medicine called a monoclonal antibody. ULTOMIRIS is used to treat adults with a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH).
It is not known if ULTOMIRIS is safe and effective in children.

Who should not receive ULTOMIRIS?

Do not start ULTOMIRIS if you have a meningococcal infection.

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

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ULTOMIRIS and other medicines can affect each other causing side effects. Know the medications you take and the vaccines you receive. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I receive ULTOMIRIS?
- ULTOMIRIS is given through a vein by intravenous (I.V.) infusion usually over about 2 hours.
- You will usually receive:
  - a starting dose of ULTOMIRIS as an infusion by your doctor, and then
  - 2 weeks later, you will start to receive an infusion of ULTOMIRIS every 8 weeks.

If you are changing treatment from SOLIRIS to ULTOMIRIS, you should receive your starting dose of ULTOMIRIS 2 weeks after your last dose of SOLIRIS.

- After each infusion, you should be monitored for at least 1 hour for allergic reactions. See “What are the possible side effects of ULTOMIRIS?”
- If you stop receiving ULTOMIRIS, your doctor 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 the number of your red blood cell count
- tiredness
- blood in your urine
- stomach-area (abdomen) pain
- low blood clots
- shortness of breath
- trouble swallowing
- erectile dysfunction (ED) in males

- If you miss an ULTOMIRIS infusion, call your doctor right away.

What are the possible side effects of ULTOMIRIS?
ULTOMIRIS can cause serious side effects including:
- See “What is the most important information I should know about ULTOMIRIS?”

Infusion reactions. Infusion reactions may happen during your ULTOMIRIS infusion. Symptoms of an infusion reaction with ULTOMIRIS may include lower back pain, pain with the infusion, or feeling faint. Tell your doctor 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
- feel faint or pass out

Your doctor will treat your symptoms as needed.

The most common side effects of ULTOMIRIS are upper respiratory infection and headache.
Tell your doctor 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 doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**General information about the safe and effective use of ULTOMIRIS.**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or doctor for information about ULTOMIRIS that is written for health professionals.

**What are the ingredients in ULTOMIRIS?**

**Active ingredient:** ravulizumab-cwvz

**Inactive ingredients:** polysorbate 80 (vegetable origin), sodium chloride, sodium phosphate dibasic, sodium phosphate monobasic, and Water for Injection

Manufactured by Alexion Pharmaceuticals, Inc., 121 Seaport Boulevard, Boston, MA 02210 USA. U.S. License Number 1743

For more information, go to www.ULTOMIRIS.com or Call: 1-888-765-4747

This Medication Guide has been approved by the U.S. Food and Drug Administration

Issued: 12/2018