INTRODUCING 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\textsuperscript{a} to treat PNH in adults

**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 18-19. Please see the accompanying full Prescribing Information and Medication Guide for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.
Understanding PNH and your management plan may help minimize the impact of PNH on your daily life.

Living with an ultra-rare disease like paroxysmal nocturnal hemoglobinuria (PNH) can be a challenge, but the more you know about PNH, the better you may be able to manage it.

What is PNH?

In PNH, a change occurs in the bone marrow stem cells, altering how red blood cells (RBCs) are made. The stem-cell change causes fewer normal cells to be made and the potentially lifelong production of “bad” cells, or PNH cells. These PNH cells are missing important protective proteins. Without these proteins, one of your body’s natural defense systems, called “complement,” destroys PNH RBCs. This destruction is known as hemolysis, the main cause of major health problems in PNH.

What is clone size?

Clone size, which is measured by high-sensitivity flow cytometry (see table to the left), is the percentage of blood cells in your body that have been affected by PNH and, therefore, do not have the protective proteins that blood cells usually have on the surface.

Many of your RBCs may be normal, but anyone with PNH will have some clones. A larger clone size means you have more of the RBCs that are missing protective proteins. But even small clone sizes can lead to PNH-related health problems—a small clone size does not necessarily mean that you have “less PNH.” Your clone size may change over time, and symptoms can get worse over time if PNH is left unmanaged. That is why continued monitoring and management are very important.

WHAT DO THE LAB RESULTS MEAN?

To find out if you have PNH, your doctor might order some lab tests to look for:

- **Evidence of elevated hemolysis with this test:** Measures LDH, an enzyme found in red blood cells. It is released during hemolysis. Knowing how much LDH is in your blood helps show how much hemolysis is happening in your body.
- **Lactate dehydrogenase (LDH) level**
  - Measures LDH, an enzyme found in red blood cells. It is released during hemolysis. Knowing how much LDH is in your blood helps show how much hemolysis is happening in your body.
- **Signs of kidney damage with this test:** Measures creatinine, which is released into the blood, to show how well your kidneys are working. The creatinine level can help indicate if and how PNH is affecting your kidneys.
- **Creatinine**
- Measures creatinine, which is released into the blood, to show how well your kidneys are working. The creatinine level can help indicate if and how PNH is affecting your kidneys.
- **Platelet levels with this test:** Measures the amount of platelets in your blood. Platelets are used for clotting and play an important role in helping you heal from injury. PNH may also affect your platelet level.
- **Platelet count**
- Measures the actual number of red and white blood cells affected by PNH in a small sample of circulating blood taken from your arm. This is the standard test for confirming whether or not you have PNH.
- **Clone size with this test:** Measures the actual number of red and white blood cells affected by PNH in a small sample of circulating blood taken from your arm. This is the standard test for confirming whether or not you have PNH. Through continued monitoring, your doctor can tell if your clone size is changing.

The tests listed in the table to the left are just some that your doctor might order. There may be others. Work closely with your doctor and keep track of your results, too.

WHAT CLONE SIZE SHOULD YOU EXPECT?

- **A small clone size** does not necessarily mean that you have “less PNH.” Your clone size may change over time, and symptoms can get worse over time if PNH is left unmanaged.

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That is why continued monitoring and management are very important.
Signs and symptoms of PNH

PNH might affect your health-related quality of life. The signs and symptoms of PNH can be tough to identify, and many are similar to those of other diseases. Symptoms might include:

- Fatigue
- Trouble swallowing (dysphagia)
- Stomach pain
- Dark-colored urine (hemoglobinuria)
- Erectile dysfunction
- Fatigue
- Trouble swallowing (dysphagia)
- Stomach pain
- Dark-colored urine (hemoglobinuria)
- Erectile dysfunction

If you have PNH, hemolysis is always taking place. Even if you can’t see or feel hemolysis, you can still have serious health problems because of it, which can include blood clots (potentially leading to stroke or heart attack), kidney disease, and/or damage to your other organs.

In this way, PNH is just like an iceberg—what you can't see or feel can hurt you the most.

PNH can be life-threatening, but there’s a lot you can do to manage it. Taking action and learning more about PNH is a good place to start.

Stay committed to your treatment and to managing your PNH.

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To watch and track your PNH, your doctor will consider all of your lab test results, signs, and symptoms

How can I help my doctor monitor my PNH?

Track your signs, symptoms, and lab results. They will show you and your doctor how you are physically affected by PNH.

Be sure to keep track of changes in your symptoms. Monitoring your symptoms is important, since PNH can manifest in serious ways. It can cause blood clots, which block veins and arteries and can lead to heart attack, stroke, and damage to your organs, as well as other problems.

Stay in touch with your physician about your PNH, especially if you experience issues with your kidneys, have had a blood clot before, or have been told you have persistent elevated LDH levels.

You don’t have to accept feeling sick

When you deal with PNH every day, over time you may learn to cope with your symptoms. For example, you might become used to feeling overly tired. But it doesn’t have to be that way. You don’t have to accept feeling sick. Your doctor can seek a treatment that is appropriate for you. That is why it is important to track your signs and symptoms, so you can tell if they’re getting worse over time instead of just accepting them. Talk to your doctor about treatment options—you shouldn’t have to feel like being sick is normal.

It’s easier to watch and track your PNH when you know how to speak with your doctor. Speak with him or her frequently, and be sure to tell the whole story.

• Tell your doctor about all of your symptoms, even if you don’t think they’re related to your PNH
• Tell your doctor when the symptoms started and how often they happen
• Show your doctor where on your body you feel your symptoms
• Describe how bad your symptoms get

Speaking with your doctor is key to successful management of PNH.

ASKING QUESTIONS WILL KEEP YOU INFORMED.

HERE ARE A FEW YOU MIGHT WANT TO ASK YOUR DOCTOR:

? Can my disease get worse over time?
? How will I know if my PNH is getting worse or better?
? I would like a copy of my lab results. Would you please help me understand them?

You and your physician can call the complimentary OneSource℠ Patient Support Program and speak with an Alexion Nurse Case Manager who can help you learn more about PNH and identify options for access to ULTOMIRIS™ (ravulizumab-cwvz).

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

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

What is ULTOMIRIS?
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.

More time between infusions with ULTOMIRIS
• ULTOMIRIS is infused every 8 weeks during the maintenance phase
  - Although infusions are less frequent with ULTOMIRIS, infusion times are longer than with eculizumab
• ULTOMIRIS needs to be infused 6-7 times a year, whereas eculizumab needs to be infused 26 times a year

Why ULTOMIRIS?
ULTOMIRIS was shown to be effective for 8 weeks in 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

Keep in mind that in PNH, your bone marrow continues to make cells that are missing protective proteins, putting PNH RBCs at constant risk of hemolysis. In some patients, in addition to making PNH cells, bone marrow may also have trouble simply making cells. This means fewer cells get produced. As a result, some patients on ULTOMIRIS still might need blood transfusions to make up for the lower number of cells.

The most common side effects of ULTOMIRIS are upper respiratory infection and headache.

INDICATION
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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
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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 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.
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- fever
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In the largest PNH trial to date, ULTOMIRIS™ (ravulizumab-cwvz) was studied in patients with PNH, including those new to treatment and those previously treated with eculizumab.

**ULTOMIRIS demonstrated comparable efficacy to eculizumab in both clinical trials**

- **In people who had no prior PNH treatment...**
  - About 7 of 10 people receiving ULTOMIRIS did not need a transfusion while receiving treatment.
  - Over half of people receiving ULTOMIRIS had levels of LDH that became normal over time.
  - People taking ULTOMIRIS had stable levels of LDH that stayed stable over time.
  - At 6 months, 68% of patients taking ULTOMIRIS had stable levels of hemoglobin (a marker of PNH activity).

- **In 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 levels of LDH that stayed stable over time.
  - 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.

- **Ask your doctor about starting or switching to ULTOMIRIS**

* The most common side effects of ULTOMIRIS are upper respiratory infection and headache.

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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.

TREATMENT CONSIDERATIONS

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<th>Lab values</th>
<th>Things to keep in mind while on treatment</th>
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<td>LDH</td>
<td>• LDH is key for tracking the level of hemolysis caused by PNH</td>
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<td></td>
<td>• It’s important to track over time to see how PNH is affecting you</td>
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<td></td>
<td>• LDH level, in comparison with your LDH level before starting ULTOMIRIS, shows how well you are responding to ULTOMIRIS; the less LDH there is, the better ULTOMIRIS is working</td>
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<tr>
<td>Hemoglobin/ anemia</td>
<td>• In PNH, even if you don’t have anemia, you might still be at risk for hemolysis and blood clots</td>
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<tr>
<td></td>
<td>• Hemoglobin is released into the bloodstream when red blood cells are destroyed by hemolysis</td>
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<td>• When outside of cells, hemoglobin is harmful and is the cause of the signs, symptoms, and serious health problems associated with PNH</td>
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<td>• Decreased hemoglobin levels during treatment do not mean protection against hemolysis</td>
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<td>• Hemoglobin levels in PNH patients with bone marrow problems might be low because of red blood cell production issues</td>
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<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>
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<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>

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 cold
• 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.

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.

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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.

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.

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

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 a 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.

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.

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

Get emergency medical care right away if you have any of these signs or symptoms and show this card.

Carry your Patient Safety Information Card now. 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.

Start carrying the card today, and carry it with you at all times during treatment and for several months after your last ULTOMIRIS dose if treatment is discontinued. Your risk of meningococcal infection may continue for several weeks after your last dose of ULTOMIRIS.

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

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PNH Resources

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.

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

Resources

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3. If you have not been vaccinated and ULTOMIRIS therapy must be started 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 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 or 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
- confusion
- eyes sensitive to light

Your doctor will give you a Patient Safety Card about your risk of meningococcal infection, as discussed above and make sure 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 genital infections. Talk to your healthcare provider to find out if you are at risk for genital infection, about genital infections and regular testing.

Your healthcare provider will give you a Patient Safety Card about your risk of infection. Talk to your healthcare provider about 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 meningococcal infection.
- if you are pregnant or plan to become pregnant. It is not known if ULTOMIRIS will harm your unborn baby.
- any breathing problems or have had breathing problems. It is not known if ULTOMIRIS will pass into your breast milk. You should not breastfeed during treatment and for 8 months after your last 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.

New 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 should start receiving 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 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 have a serious infusion reaction, including:

  - chills
  - trouble breathing or shortness of breath
  - swelling of your face, tongue, or throat
  - fast heart rate 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. Please see the accompanying full Prescribing Information and Medication Guide for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections.
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.

Bone marrow: Soft tissue inside your large bones. Stem cells, contained in your bone marrow, work to create parts of your blood: red blood cells, white blood cells, and platelets.

Breakthrough events: Breakthrough events, or breakthrough hemolysis, are defined as at least 1 new or worsening symptom or sign 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.

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.

Erectile dysfunction: A condition found in men that affects their ability to achieve or maintain an erection.

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 cells 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.

Progressive: A progressive disease is one that gets worse over time.

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.

White blood cells: A type of cell found in your blood that helps your immune system fight disease and infection.
We understand that managing PNH can be difficult, but you are not alone

Staying on an effective treatment plan and continuing to educate yourself can help you manage PNH.

Stay committed
PNH is a lifelong disease that requires a steady commitment. ULTOMIRIS™ (ravulizumab-cwvz) provides long-acting control, so it’s important to stay with your treatment, even when you are feeling better, unless your doctor decides you need a change.

Talk to your doctor
Sometimes the signs and symptoms of PNH may become more intense or come and go, but this doesn’t necessarily mean ULTOMIRIS isn’t working. Take note whenever you experience a change in your health and talk to your doctor.

Keep track
Keeping track of your symptoms and lab results will help your doctor understand how you are doing. It will also help show how you’re progressing with ULTOMIRIS.

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

Stay committed to your treatment and to managing your PNH. Discover more resources and information at www.ULTOMIRIS.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 18-19. Please see the accompanying full Prescribing Information and Medication Guide for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.
The recommended dosing regimen for adult patients (≥ 18 years of age) with PNH consists of a loading dose of ULTOMIRIS, 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.

Table 1: ULTOMIRIS Weight-Based Dosing Regimen

<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).

DOSAGE AND ADMINISTRATION

Full Prescribing Information: CONTENTS*

1 INSTRUCTIONS AND USAGE

1. ULTOMIRIS is a complement inhibitor indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH). (1)

2. DOSE AND ADMINISTRATION

2.1 Recommended Vaccination and Prophylaxis

Vaccine patients for meningococcal disease according to current ACIP guidelines to reduce the risk of developing a meningococcal infection. (See Warnings and Precautions (5.1) for additional guidance on the management of the risk of meningococcal infection. Vaccination reduces, but does not eliminate, the risk of meningococcal infection.

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

<table>
<thead>
<tr>
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</tr>
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<tbody>
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<td>3,000</td>
</tr>
<tr>
<td>greater than or equal to 60 to less than 100</td>
<td>2,700</td>
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</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).

DOSAGE FORMS AND STRENGTHS

Injection: 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).

WARNINGS AND PRECAUTIONS

Use caution when administering ULTOMIRIS to patients with any other systemic infection (5.2).

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

*Sections or subsections omitted from the full prescribing information are not listed
3. DOSAGE FORMS AND STRENGTHS

Injection: 300 mg/30 mL (10 mg/mL) as a clear to translucent, slightwhitish 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. Vaccine 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. Immune 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 antibiotic 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 sites 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.

6. ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling.

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 serious adverse drug reactions (â‰¥10%) with ULTOMIRIS were upper respiratory tract infection and headache.

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>Diarrhea</td>
<td>19 (9)</td>
<td>12 (5)</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>19 (9)</td>
<td>19 (9)</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>13 (6)</td>
<td>16 (7)</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Pyrexia</td>
<td>15 (7)</td>
<td>18 (8)</td>
</tr>
<tr>
<td></td>
<td>Infections and Infestations</td>
<td>Upper respiratory tract infection*</td>
<td>86 (39)</td>
</tr>
<tr>
<td></td>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>Pain in extremity</td>
<td>14 (6)</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>11 (5)</td>
<td>12 (5)</td>
</tr>
<tr>
<td></td>
<td>Nervous System Disorders</td>
<td>Headache</td>
<td>71 (32)</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>12 (5)</td>
<td>14 (6)</td>
</tr>
</tbody>
</table>

\* Graded terms included: Nasopharyngitis, Upper respiratory tract infection, Oropharyngeal pain, Viral upper respiratory tract infection, Rhinitis, Respiratory tract infection, Rhinorrhea, Pharyngitis, and Upper respiratory tract inflammation.

5.2 Other Infections

ULTOMIRIS blocks terminal complement activation; therefore, patients may have increased susceptibility to encapsulated bacteria infections, especially infections caused by Neisseria meningitidis but also Streptococcus pneumoniae, Haemophilus influenzae, and to a lesser extent, Neisseria gonorrhoeae. If ULTOMIRIS therapy is administered to patients with active systemic infections, monitor closely for signs and symptoms of worsening infection.

5.3 Monitoring Disease Manifestations after ULTOMIRIS Discontinuation

After discontinuing treatment with ULTOMIRIS, closely monitor for signs and symptoms of hemolysis, identified by elevated LDH along with sudden decrease in PNH clone size or hemoglobin, or re-appearance of symptoms such as fatigue, hemoglobinuria, abdominal pain, or respiratory compromise. If these symptoms are of concern, major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction. Monitor any patient who discontinues ULTOMIRIS for at least 16 weeks to detect hemolysis and other reactions. If signs and symptoms of hemolysis occur after discontinuation, including elevated LDH, consider restarting treatment with ULTOMIRIS.

5.4 Thromboembolic Event Management

The effect of withdrawal of anticoagulant therapy during ULTOMIRIS treatment has not been established. Therefore, treatment with ULTOMIRIS should not after anticoagulant management.

5.5 Infusion Reactions

Administration of ULTOMIRIS may in result in infusion reactions. In clinical trials, 3 out of 222 patients with PNH treated with ULTOMIRIS experienced infusion reactions (lower back pain, drop in blood pressure and infusion-related pain) during ULTOMIRIS administration. This reactions did not require discontinuation of ULTOMIRIS. Interrupt ULTOMIRIS infusion and institute appropriate supportive measures if signs of cardiovascular instability or respiratory compromise occur.
Complement Inhibitor-Naïve and Patients Previously Treated with Eculizumab

<table>
<thead>
<tr>
<th>N</th>
<th>Complement Inhibitor-Naïve</th>
<th>N</th>
<th>Previously Treated with Eculizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>LD</td>
<td>125</td>
<td>771 ± 166 (21.5)</td>
<td>95</td>
</tr>
<tr>
<td>MD</td>
<td>124</td>
<td>1379 ± 276 (20.0)</td>
<td>95</td>
</tr>
</tbody>
</table>

C\text{PDB} \text{ (mcg/mL)}

| LD | 125 | 391 ± 137 (35.0) | 96 | 405 ± 121 (29.9) |
| MD | 124 | 473 ± 158 (33.4) | 95 | 501 ± 143 (28.6) |

Distribution

The mean (SD) volume of distribution at steady state was 5.34 (0.92) L.

Elimination

The mean (SD) terminal elimination half-life and clearance of ravulizumab-cwz in patients with PNH are 49.7 (8.9) days and 0.08 (0.022) L/day respectively.

Specific Populations

No clinically significant differences in the pharmacokinetics of ravulizumab-cwz were observed based on sex, age (18 to 83 years), race, hepatic impairment, or mild to moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m\(^2\), estimated by MDRD). The effect of severe renal impairment (eGFR 15 to 29 mL/min/1.73 m\(^2\), estimated by MDRD) on ravulizumab-cwz pharmacokinetics is unknown.

Body weight was a significant covariate on the pharmacokinetics of ravulizumab-cwz.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal carcinogenicity studies of ravulizumab-cwz have not been conducted. Genotoxicity studies have not been conducted with ravulizumab-cwz.

Effects of ravulizumab-cwz upon fertility have not been studied in animals. Intrauterine injections of male and female mice with a murine anti-C5 antibody at up to 0.8-2.2 times the equivalent of the clinical dose of ULTOMIRIS had no adverse effects on mating or fertility.

14 CLINICAL STUDIES

The safety and efficacy of ULTOMIRIS in patients with PNH was assessed in two open-label, randomized, active-controlled, non-inferiority Phase 3 studies: PNH Study 301 and PNH Study 302. Study 301 enrolled patients with PNH who were complement inhibitor naïve and had active hemolysis. Study 302 enrolled patients with PNH who were clinically stable after having been treated with eculizumab for at least the past 6 months.

In both studies, ULTOMIRIS was dosed intravenously in accordance with the weight-based dosing described in Section 2.1 (4 infusions of ULTOMIRIS over 26 weeks) above. Eculizumab was administered on Days 1, 8, 15, and 22, followed by maintenance treatment with 900 mg of eculizumab on Day 29 and every 2 weeks (q2w) thereafter for a total of 26 weeks of treatment, according to the approved dosing regimen of eculizumab which was the standard-of-care for PNH at the time of studies.

Patients were vaccinated against meningococcal infection prior to or at the time of initiating treatment with ULTOMIRIS or eculizumab, or received prophylactic treatment with appropriate antibiotics 2 weeks after vaccination. Prophylactic treatment with appropriate antibiotics beyond 2 weeks after vaccination was at the discretion of the provider.

14.1 Study in Complement-Inhibitor Naïve Patients with PNH

The Complement-Inhibitor Naïve Study [ALXN1210-PNH-301; NCT02946463] was a 26-week, multicenter, open-label, randomized, active-controlled, non-inferiority Phase 3 study conducted in 246 patients naïve to complement inhibitor treatment prior to study entry.

Patients with PNH with flow cytometric confirmation of at least 5% PNH GIMs were randomized 1:1 to either ULTOMIRIS or eculizumab. The mean total PNH granulocyte clone size was 85%, the mean total PNH monocyte clone size was 98%, and the mean total PNH RBC clone size was 39%. Ninety-eight percent of patients had a documented PNH-associated condition diagnosed prior to enrollment on the trial: anemia (85%), hemoglobinuria (63%), history of aplastic anemia (32%), history of renal failure (12%), myelodysplastic syndrome (5%), pregnancy (3%), and other (16%). Major baseline characteristics were balanced between treatment groups.

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

<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)</td>
<td>Min, max</td>
<td>44.2 (7.5)</td>
</tr>
<tr>
<td>Race</td>
<td>n (%)</td>
<td>65 (52.0)</td>
<td>69 (57.0)</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>n (%)</td>
<td>43 (34.4)</td>
<td>51 (42.1)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>n (%)</td>
<td>2 (1.6)</td>
<td>4 (3.3)</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>n (%)</td>
<td>1 (0.8)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Other</td>
<td>n (%)</td>
<td>4 (3.2)</td>
<td>4 (3.3)</td>
</tr>
<tr>
<td>Not reported</td>
<td>n (%)</td>
<td>3 (2.4)</td>
<td>4 (3.3)</td>
</tr>
<tr>
<td>Pre-treatment LDH levels (U/L)</td>
<td>Median</td>
<td>Min, max</td>
<td>1513.5 (378.0, 3759.5)</td>
</tr>
<tr>
<td>Units of PRBC/whole blood transfused within 12 months prior to first dose</td>
<td>Median</td>
<td>Min, max</td>
<td>6.0 (1.44)</td>
</tr>
<tr>
<td>Antibody reactive agents used within 28 days prior to first dose</td>
<td>n (%)</td>
<td>22 (17.9)</td>
<td>22 (18.5)</td>
</tr>
<tr>
<td>Patients with a history of MAWE*</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>

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

MAWE = 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 x ULN, after prior LDH reduction to < 1.5 x ULN on therapy and the proportion of patients with stabilized hemoglobin.

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

<table>
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</tr>
</tbody>
</table>

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

MAWE = major adverse vascular event
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>73.8%</td>
<td>66.1%</td>
<td>Difference in rate</td>
<td>6.8 (-4.6, 18.14)</td>
</tr>
<tr>
<td>LDH normalization</td>
<td>53.6%</td>
<td>49.4%</td>
<td>Odds ratio</td>
<td>1.19 (0.80, 1.77)</td>
</tr>
<tr>
<td>LDH percent change</td>
<td>-76.84%</td>
<td>-76.02%</td>
<td>Difference in % change</td>
<td>-0.83 (-5.21, 3.56)</td>
</tr>
<tr>
<td>Breakthrough hemolysis</td>
<td>4.0%</td>
<td>10.7%</td>
<td>Difference in rate</td>
<td>6.7 (-14.21, 0.18)</td>
</tr>
<tr>
<td>Hemoglobin stabilization</td>
<td>68.0%</td>
<td>64.5%</td>
<td>Difference in rate</td>
<td>2.9 (-8.80, 1.64)</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 in percent within 26 weeks prior to receiving the first dose of ULTOMIRIS, if they have not previously been vaccinated. They are required to be reconstituted according to current medical guidelines for meningococcal vaccines use while on ULTOMIRIS therapy. Inform patients that vaccination may not prevent meningococcal infection. Inform patients about the signs and symptoms of meningococcal infection/sepsis, and strongly advise patients to seek immediate medical attention if these signs or symptoms occur. These signs and symptoms are as follows:

- headache with nausea or vomiting
- headache and a fever
- headache with a stiff neck or stiff back
- fever
- fever and a rash
- confusion
- muscle aches with flu-like symptoms
- eyes sensitive to light

Inform patients that they will be given an ULTOMIRIS Patient Safety Card that they should carry with them at all times. This card describes symptoms which, if experienced, should prompt the patient to immediately seek medical evaluation.

Other infections

Counsel patients of the increased risk of infections, particularly those due to encapsulated bacteria, especially Neisseria species. Advise patients of the need for vaccination against meningococcal infections according to current medical guidelines. Counsel patients about gonorrhea prevention and advise regular testing for patients at risk. Advise patients to report any new signs and symptoms of infection.

Discontinuation

Inform patients with PNH that they may develop hemolysis due to PNH when ULTOMIRIS is discontinued and that they will be monitored by their healthcare professional for at least 16 weeks following ULTOMIRIS discontinuation.

Inform patients who discontinue ULTOMIRIS to keep the ULTOMIRIS Patient Safety Card with them for eight months after the last ULTOMIRIS dose, because the increased risk of meningococcal infection persists for several weeks following discontinuation of ULTOMIRIS.

Infusion reactions

Advise patients that administration of ULTOMIRIS may result in infusion reactions.

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US License Number 1743

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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 8: Baseline Characteristics in Eculizumab-Experienced Patients with PNH

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Statistics</th>
<th>ULTOMIRIS (n = 97)</th>
<th>Eculizumab (n = 98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) at first infusion in study</td>
<td>Mean (SD) Min, max</td>
<td>46.6 (14.41) 18, 79</td>
<td>48.8 (13.97) 23, 77</td>
</tr>
<tr>
<td>Race</td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>50 (51.5)</td>
<td>61 (62.2)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>23 (23.7)</td>
<td>19 (19.4)</td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>5 (5.2)</td>
<td>3 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (2.1)</td>
<td>1 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Not reported</td>
<td>13 (13.4)</td>
<td>13 (13.3)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (3.1)</td>
<td>1 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Multiple</td>
<td>1 (1.0)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>50 (51.5)</td>
<td>48 (49.0)</td>
<td></td>
</tr>
<tr>
<td>Pre-treatment LDH levels (U/L)</td>
<td>Median Min, max</td>
<td>234.0 135.0, 383.5</td>
<td>234.0 100.0, 365.5</td>
</tr>
<tr>
<td>Units of pRBC/whole blood transfused within 12 months prior to first dose</td>
<td>Median Min, max</td>
<td>4.0 1, 32</td>
<td>2.5 (2, 15)</td>
</tr>
<tr>
<td>Antithrombotic agents used within 28 days prior to first dose</td>
<td>n (%)</td>
<td>20 (20.6) 13 (13.3)</td>
<td></td>
</tr>
<tr>
<td>Patients with a history of MAVe*</td>
<td>n (%)</td>
<td>28 (28.9) 22 (22.4)</td>
<td></td>
</tr>
<tr>
<td>Patients with a history of thrombosis</td>
<td>n (%)</td>
<td>27 (27.8) 21 (21.4)</td>
<td></td>
</tr>
<tr>
<td>Patients with concomitant anticoagulant treatment</td>
<td>n (%)</td>
<td>22 (22.7) 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>8.4%</td>
<td>Difference in % change</td>
<td>9.2 (-0.42, 18.8)</td>
</tr>
<tr>
<td>Breakthrough hemolysis</td>
<td>0%</td>
<td>5.1%</td>
<td>Difference in rate</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 rate</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 rate</td>
<td>1.4 (-10.4, 13.3)</td>
</tr>
</tbody>
</table>

Note: CI = confidence interval
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 and fever
   - headache with a stiff neck or stiff back
   - fever
   - fever and 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 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.

What is the most important information I should know about 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
- 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

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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

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