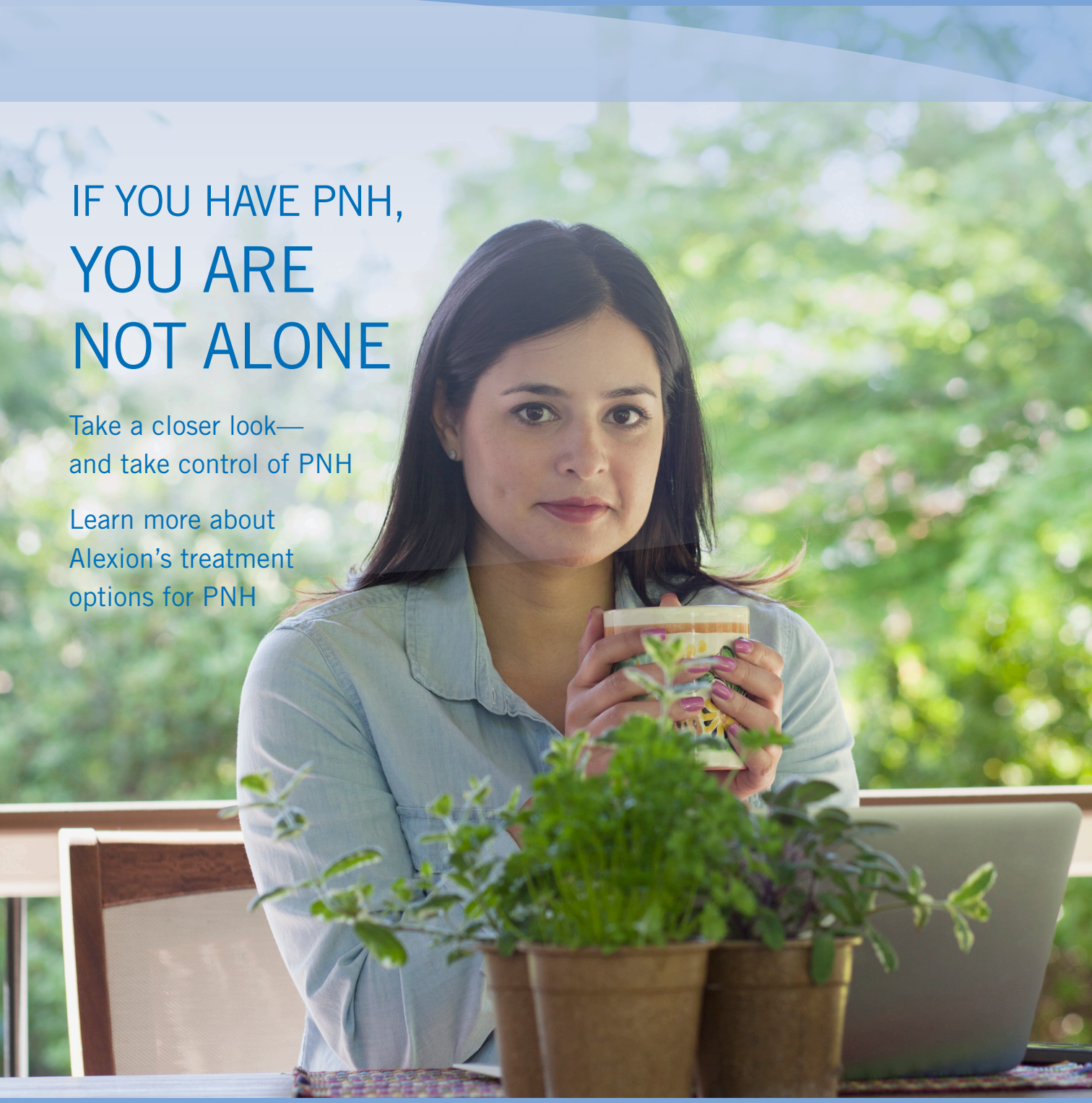


IF YOU HAVE PNH, YOU ARE NOT ALONE

Take a closer look—
and take control of PNH

Learn more about
Alexion's treatment
options for PNH

INDICATION & SELECT IMPORTANT SAFETY INFORMATION FOR SOLIRIS

INDICATION

What is SOLIRIS?

SOLIRIS is a prescription medicine called a monoclonal antibody. SOLIRIS is used to treat: patients with a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH).

It is not known if SOLIRIS is safe and effective in children with PNH.

SELECT IMPORTANT SAFETY INFORMATION

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

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

- **SOLIRIS 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 SOLIRIS if you have not already had this vaccine.
  2. If your doctor decided that urgent treatment with SOLIRIS is needed, you should receive meningococcal vaccination as soon as possible.
  3. If you have not been vaccinated and SOLIRIS 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 SOLIRIS. 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, confusion, muscle aches with flu-like symptoms, eyes sensitive to light.

SOLIRIS®
(eculizumab)
Injection for Intravenous Use
300 mg/30 mL vial

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

Please see Indication and Important Safety Information on pages 20-22.

PNH is a serious disease, but you can manage it

Paroxysmal nocturnal hemoglobinuria (PNH) is an ultra-rare, progressive, chronic, and systemic disease connected with serious health problems, but it can be treated. This brochure can help you learn about PNH and how Soliris can work to treat it, and it will answer the following questions:

- What is PNH and what causes it?
- How is PNH diagnosed?
- What do my lab results mean?
- What is Soliris?
- What do I need to know before taking Soliris?
- How is Soliris given?
- What should I know about the risk of infection?
- Where can I find out more?

Living with an ultra-rare disease, like PNH, can be a challenge, but the more you know about PNH, the better you will be able to manage it.

The best way to manage PNH is to learn all you can about it, work with your doctor, and commit to your management plan.

Staying educated to better manage PNH

In addition to this brochure, there are free resources to help you keep informed about PNH and connect you with other people who are also living with the disease:

- OneSource™: If you have PNH, you are not alone. OneSource™ is available at no cost to people living with PNH. You'll get one-to-one support from an Alexion Case Manager who is knowledgeable in insurance matters. OneSource™ can help you learn about PNH, assist with identifying access options, and give ongoing support resources for people living with PNH and those who care for them. And, if you would like an Alexion Case Manager to put you in touch with other people just like you who are living with PNH, just ask. Connect with an Alexion Case Manager, with no obligation, by calling 1.888.765.4747 or visiting alexiononesource.com.
- National Organization for Rare Disorders (NORD): A not-for-profit organization dedicated to helping people with rare disorders, such as PNH—www.rarediseases.org (this web address will take you to an external site to which Alexion's privacy policy does not apply. Alexion Pharmaceuticals, Inc., provides information about other websites as a convenience. Alexion does not endorse, cannot control, and is not responsible for the content of any other sites.)

As you are reading, you can find the definitions to underlined terms in the glossary on pages 30-31.

You and your physician can talk to a OneSource™ Alexion Case Manager for free to learn more about your disease, resources that are available, and support regarding financial information or coverage.

Call 1.888.765.4747 or visit alexiononesource.com.

ONESOURCE™
Personalized Patient Support from Alexion

Understanding PNH and your management plan can help minimize the impact of PNH on your daily life

What is PNH?

PNH is an acquired disease, which means it is not inherited but rather develops in some people over time. Anyone can get PNH, and once it occurs, it remains for life in most patients. PNH destroys an important part of your blood—the red blood cells (RBCs)—and can be life-threatening. PNH can occur at any age, but the average age at diagnosis is in the early 30s.

In PNH, a change occurs in the stem cells in the body, including in the bone marrow, where red blood cells are made. The stem cell change causes fewer normal cells to be made and the lifelong production of "bad" cells, or PNH cells. These PNH cells are missing important protective proteins. Without the proteins, one of your body's natural defense systems, complement, destroys PNH RBCs. This destruction is known as hemolysis, the main cause of major health problems in PNH, including some that are life-threatening. If you have PNH, you are at constant risk of hemolysis.

How is PNH diagnosed, and 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	
Lactate dehydrogenase (LDH) level	Measures LDH, an enzyme found in RBCs that 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	
Creatinine	Measures creatinine, a waste product in the blood, to show how well your kidneys are working.
Platelet levels with this test	
Platelet count	Measures the amount of platelets in your blood. Platelets are used for clotting and play an important role in helping you heal from injury.
Clone size with this test	
High-sensitivity flow cytometry	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 increasing.

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

Please see Indication and Important Safety Information on pages 20-22.

Clone size, which is measured by high-sensitivity flow cytometry (see table on page 4), 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 will 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 grow over time, so symptoms can get worse over time if PNH is left unmanaged. That is why continued monitoring is very important.

Because everyone is different, lab results and how each person experiences the disease might be different, too.

The tests listed in the table on page 4 are just some that your doctor might order. There can be others. Work closely with him or her and keep track of those results, too.

You and your physician can talk to a OneSource™ Alexion Case Manager for free to learn more about your disease, resources that are available, and support regarding financial information or coverage.

Call 1.888.765.4747 or visit alexiononesource.com.

ONESOURCE™
Personalized Patient Support from Alexion

Understanding PNH and your management plan can help minimize the impact of PNH on your daily life (continued)

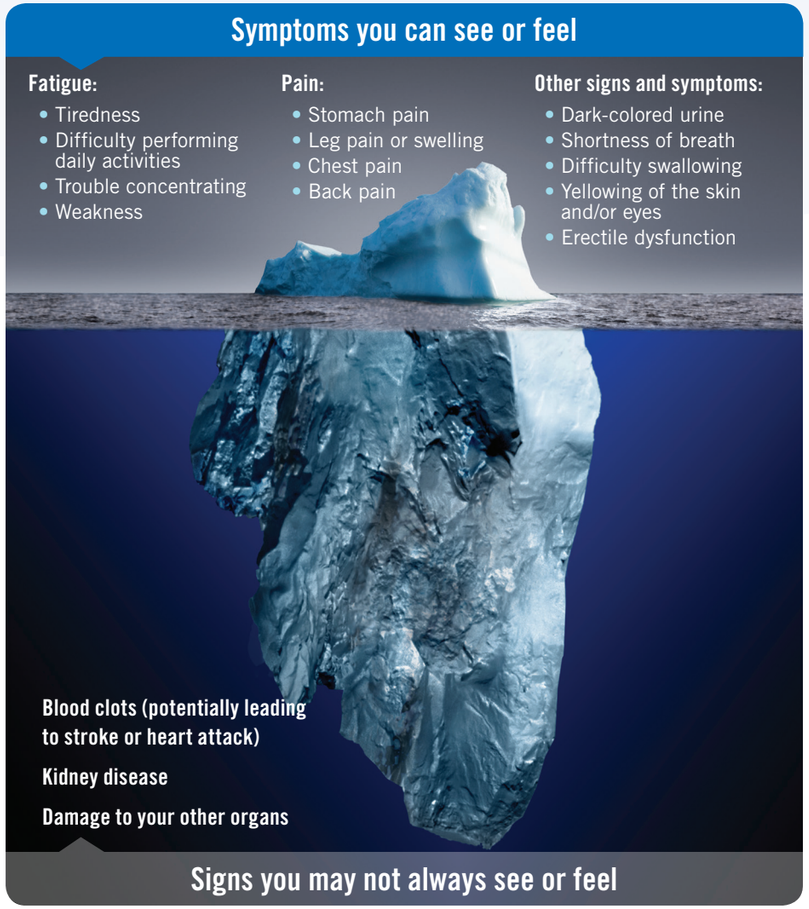
What are the effects of PNH?

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 other diseases. Some symptoms might include:

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

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.

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

Please see Indication and Important Safety Information on pages 20-22.

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You and your physician can talk to a OneSource™ Alexion Case Manager for free to learn more about your disease, resources that are available, and support regarding financial information or coverage.

Call 1.888.765.4747 or visit Soliris.net/patients/one-source.

ONESOURCE™
Personalized Patient Support from Alexion

US/SOL-P/0024

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 the full story of how you are physically affected by PNH. In the pocket at the end of this brochure there is a form that will help you keep track of your labs and symptoms.

Be sure to keep track of changes in your symptoms. Monitoring your symptoms is important, because 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.

If you experience issues with your kidneys, have had a blood clot before, or have been told you have persistent elevated LDH, you should remain in touch with your doctor.

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, being overly tired might become the way you are used to feeling. But it may not have to be that way. You don't have to accept feeling sick. 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 management options—you shouldn't have to feel like being sick is normal.

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

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 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
- In addition to your prescription medicines, let them know any vitamins, supplements or over-the-counter medicines you are taking

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 test results. Would you please help me understand them?

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

Please see Indication and Important Safety Information on pages 20-22.

You and your physician can talk to a OneSource™ Alexion Case Manager for free to learn more about your disease, resources that are available, and support regarding financial information or coverage.

Call 1.888.765.4747 or visit alexiononesource.com.

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Soliris is approved by the FDA to treat patients with PNH

What is Soliris?

- Soliris is a complement inhibitor indicated for the treatment of patients with PNH to reduce hemolysis
- Soliris is a prescription medicine called a humanized monoclonal antibody, which is a protein that your body recognizes as natural
- Soliris works by blocking complement (part of your body's defense system) from attacking your RBCs
  - Soliris can lower the ability of your immune system to fight infections

By reducing ongoing hemolysis, Soliris may help reduce fatigue and improve health-related quality of life.

SELECT IMPORTANT SAFETY INFORMATION

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

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

- **SOLIRIS 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 SOLIRIS if you have not already had this vaccine.
2. If your doctor decided that urgent treatment with SOLIRIS is needed, you should receive meningococcal vaccination as soon as possible.
3. If you have not been vaccinated and SOLIRIS 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 SOLIRIS. 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, confusion, muscle aches with flu-like symptoms, eyes sensitive to light.

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Call 1.888.765.4747 or visit alexiononesource.com.

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What are your treatment options?

Your doctor may recommend additional treatments for your PNH, such as:

- Anticoagulants (blood thinners)
- Blood transfusions
- Corticosteroids
- RBC supplements

However, these types of treatment do not address chronic hemolysis, the underlying cause of PNH. Results for each PNH patient on Soliris may be different, so the improvements you see in your health and your experiences with your therapy may differ from others.

Soliris was shown to be effective in two clinical studies. Patients with PNH experienced the following:

- 87% reduction in hemolysis, as measured by LDH
- 92% overall reduction in blood clots—one of the serious health problems with PNH
- 94% fewer blood clots in patients with PNH who received anticoagulants before and during treatment with Soliris
- Reduced fatigue and improved health-related quality of life after 3 weeks of treatment

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 addition to making PNH cells, your bone marrow may also have trouble simply making cells. This means fewer cells get produced. As a result, some patients on Soliris still might need blood transfusions to make up for the lower number of cells.

Common side effects in people with PNH treated with Soliris include: headaches, runny nose and colds, sore throat, back pain, and nausea.

In Soliris clinical trials, most people also received blood-thinning medicine. The effect of stopping blood-thinning medicine during treatment with Soliris has not been studied. Therefore, treatment with Soliris should not alter anticoagulant management.

Speak with your doctor about how Soliris can help in the treatment of PNH.

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

Please see Indication and Important Safety Information on pages 20-22.

SOLIRIS®
(eculizumab)
Injection for Intravenous Use

US/SOL-P/0024

Helpful information about Soliris

What do I need to know before taking Soliris?

Soliris is a medicine that affects your immune system. Soliris can lower the ability of your immune system to fight infections. Soliris increases your chance of getting serious and life-threatening meningococcal infections. You must receive meningococcal vaccination at least 2 weeks before your first dose of Soliris unless you have already had this vaccine. If your doctor decides that urgent treatment with Soliris is needed, you should receive meningococcal vaccination as soon as possible.

For Soliris to reduce hemolysis, the drug needs to stay above a certain level in your blood. However, like all drugs, Soliris 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 Soliris is about 11 days. A regular therapy schedule keeps Soliris in your body at a level where it works best.

Soliris should be infused according to the recommended dosing schedule for you to get the most out of your treatment. If the level of Soliris in your body gets too low, hemolysis can occur.

Hemolysis is the underlying cause of the major health problems in PNH. Missing doses can cause hemolysis to happen. Work closely with your doctor to best manage PNH.

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

Treatment considerations

Lab values	Things to keep in mind while on treatment	Are laboratory tests useful in determining your response to treatment in reducing hemolysis?
LDH	• LDH is key for tracking the level of hemolysis caused by PNH • It's important to track over time to see how PNH is affecting you • LDH level, in comparison with your LDH level before starting Soliris, shows how well you are responding to Soliris; the less LDH there is, the better Soliris is working	☒ Yes ☐ No
Hemoglobin/ Anemia	• In PNH, even if you don't have anemia, you might still be at risk of hemolysis and blood clots • Hemoglobin is released into the bloodstream when RBCs are destroyed by hemolysis • When outside of cells, hemoglobin is harmful and is the cause of the signs, symptoms, and serious health problems associated with PNH • Increased hemoglobin levels during treatment do not mean protection against hemolysis • Hemoglobin levels in PNH patients with bone marrow problems might be low because of RBC production issues	☐ Yes ☒ No
Platelet counts	• Your platelet count might stay the same even after months of treatment, regardless of a decrease in LDH level and need for blood transfusions	☐ Yes ☒ No
Transfusion requirements	• Transfusions may still be necessary for patients with bone marrow issues, because Soliris only treats hemolysis and not RBC production issues	☐ Yes ☒ No

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

Please see Indication and Important Safety Information on pages 20-22.

SOLIRIS® (eculizumab) Injection for Intravenous Use

US/SOL-P/0024

Helpful information about Soliris

How is Soliris given?

For Soliris to work properly, the way that it is given to you is important:

- Soliris is given as an infusion into a vein in your hand or arm
- The actual infusion generally takes about 35 minutes in adults
- You will start with weekly dosing for the first 5 weeks
- Then you will receive an infusion every 2 weeks

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

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

Your infusions should take place at a location that is convenient for you. Infusions must be given by trained health care professionals, usually at a doctor's office, health clinic, or infusion center. For the hour following your infusion, you may be monitored for allergic reaction.

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 or nursing—find out about the risks and benefits of treatment with Soliris
- About the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements

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Call 1.888.765.4747 or visit Soliris.net/patients/one-source.

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You must receive meningococcal vaccination at least 2 weeks before your first dose of Soliris, unless you have already received this vaccine

Get vaccinated. Soliris can lower the ability of your immune system to fight some bacterial infections. Before taking Soliris 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 Soliris is needed, you should get the meningococcal vaccine as soon as possible.

If you had a meningococcal vaccine in the past, you might need a booster dose before starting Soliris. Your doctor will decide if you need another dose of a meningococcal vaccine.

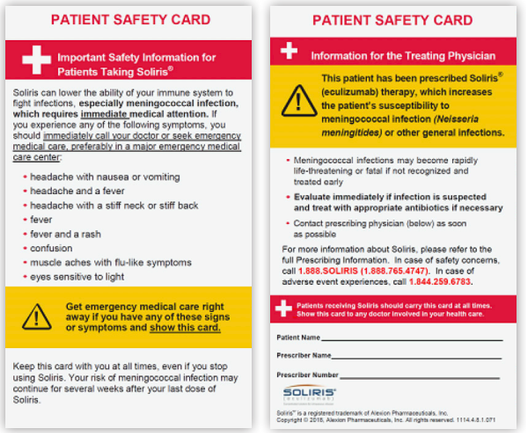
What are the symptoms of meningococcal infection?

The same mechanism that Soliris uses to stop hemolysis can increase your risk of getting an infection, especially meningococcal infection. **Call your doctor or get emergency medical care right away if you get any of these signs or symptoms of 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, and eye sensitivity to light.

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 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 3 months after your last Soliris dose, if treatment is discontinued. Your risk of meningococcal infection may continue for several weeks after your last dose of Soliris.

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


PATIENT SAFETY CARD

Important Safety Information for Patients Taking Soliris®

Soliris can lower the ability of your immune system to fight infections, **especially meningococcal infection, which requires immediate medical attention.** If you experience any of the following symptoms, you should immediately call your doctor or seek emergency medical care, preferably in a major emergency medical care center:

- 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.

Keep this card with you at all times, even if you stop using Soliris. Your risk of meningococcal infection may continue for several weeks after your last dose of Soliris.

PATIENT SAFETY CARD

Information for the Treating Physician

This patient has been prescribed Soliris® (eculizumab) therapy, which increases the patient's susceptibility to meningococcal infection *(Neisseria meningitidies)* or other general infections.

- Meningococcal infections may become rapidly life-threatening or fatal if not recognized and treated early
- **Evaluate immediately if infection is suspected and treat with appropriate antibiotics if necessary**
- Contact prescribing physician (below) as soon as possible

For more information about Soliris, please refer to the full Prescribing Information. In case of safety concerns, call **1.888.SOLIRIS (1.888.765.4747)**. In case of adverse event experiences, call **1.844.259.6783**.

Patients receiving Soliris should carry this card at all times. Show this card to any doctor involved in your health care.

Patient Name_____

Prescriber Name_____

Prescriber Number_____

SOLIRIS®

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

Please see Indication and Important Safety Information on pages 20-22.

SOLIRIS® (eculizumab)
Injection for Intravenous Use

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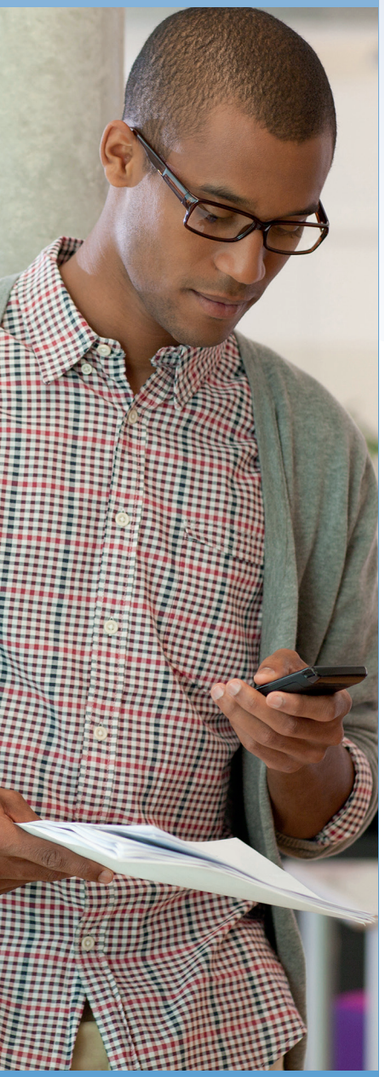

Resources to make your PNH experience a little easier

Soliris is only available through a program called the Soliris Risk Evaluation and Mitigation Strategy (REMS)

Before you can receive Soliris, your doctor must:

- [X] Enroll in the Soliris REMS program
- [X] Counsel you about the risk of meningococcal infection
- [X] Give you information about the symptoms of meningococcal infection
- [X] Give you a **Patient Safety Card** about your risk of meningococcal infection
- [X] Make sure that you are vaccinated with a meningococcal vaccine

Soliris may also increase the risk of other types of serious infections.
If your child is treated with Soliris, make sure that your child receives vaccinations against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib).

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 still

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

To manage PNH better, learn all you can about the disease, work closely with your doctor, and take Soliris according to your dosing schedule.

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

Please see Indication and Important Safety Information on pages 20-22.

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You and your physician can talk to a OneSource™ Alexion Case Manager for free to learn more about your disease, resources that are available, and support regarding financial information or coverage.

Call 1.888.765.4747 or visit alexiononesource.com.

SOLIRIS®
(eculizumab)
Injection for Intravenous Use

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Resources (continued)

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, advice, and support.

- OneSource™: Available from Alexion at no cost to people living with PNH. You'll get one-to-one support from an Alexion Case Manager who is knowledgeable in insurance matters. OneSource™ can help you learn about PNH, help you identify options for access to Soliris, and give ongoing support for people living with PNH and those who care for them. And, through the Buddy Program, an Alexion 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
- 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
- PNH Community: A patient support site in partnership with National Organization for Rare Disorders (NORD) and the Aplastic Anemia & MDS International Foundation (AA & MDSIF). This site helps PNH patients connect with others who are living with the disease. It also helps them gain access to many free events offered throughout the country
- PNH Research and Support Foundation: A volunteer-based organization that helps raise money for PNH research and offers limited financial support for PNH-related expenses to qualified applicants

Alexion provides a list of resources as a courtesy and is not responsible for the content provided by those resources.

To learn more about PNH, visit Soliris.net

ONESOURCE™
Personalized Patient Support from Alexion

Call 1.888.765.4747 or visit alexiononesource.com.

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PNH management and Soliris

If you have PNH, it means your bone marrow is creating RBCs that are at constant risk of hemolysis. Staying on an effective treatment plan and continuing to educate yourself will help you manage PNH.

Stay committed

PNH is a lifelong disease that takes steady commitment. For Soliris to keep working, maintain adherence to the prescribed dosing schedule, unless your doctor decides a change is necessary.

Take note

Sometimes the signs and symptoms of PNH become more intense or come and go. This can be a short-term change and does not necessarily mean Soliris is not working. Note any time you experience a change in your health and tell your doctor.

Keep track

Keeping track of your signs, symptoms, and lab results will show you the full story of how you are physically affected by PNH. It will also show your progress with Soliris.

Discover more resources and find steps you can take to help manage your PNH at Soliris.net

You and your physician can talk to a OneSource™ Alexion Case Manager for free to learn more about your disease, resources that are available, and support regarding financial information or coverage.

Call 1.888.765.4747 or visit Soliris.net/patients/one-source.

SOLIRIS®
(eculizumab)
Injection for Intravenous Use

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Indication and Important Safety Information for Soliris

INDICATION

What is SOLIRIS?

SOLIRIS is a prescription medicine called a monoclonal antibody. SOLIRIS is used to treat patients with a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH).

It is not known if SOLIRIS is safe and effective in children with PNH.

IMPORTANT SAFETY INFORMATION

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

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

- **SOLIRIS 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 SOLIRIS if you have not already had this vaccine.
2. If your doctor decided that urgent treatment with SOLIRIS is needed, you should receive meningococcal vaccination as soon as possible.
3. If you have not been vaccinated and SOLIRIS 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 SOLIRIS. 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, confusion, 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 3 months after your last SOLIRIS dose. Your risk of meningococcal infection may continue for several weeks after your last dose of SOLIRIS. It is important to show this card to any doctor or nurse who treats you. This will help them diagnose and treat you quickly.

Important Safety Information for Soliris (continued)

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

- enroll in the SOLIRIS 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

SOLIRIS may also increase the risk of other types of serious infections. If your child is treated with SOLIRIS, make sure that your child receives vaccinations against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib). Certain people may be at risk of serious infections with gonorrhea. Talk to your doctor about whether you are at risk for gonorrhea infection, about gonorrhea prevention, and regular testing. Certain fungal infections (*aspergillus*) may also happen if you take SOLIRIS and have a weak immune system or a low white blood cell count.

Who should not receive SOLIRIS?

Do not receive SOLIRIS if you:

- have a meningococcal infection
- have not been vaccinated against meningitis infection unless your doctor decides that urgent treatment with SOLIRIS is needed. See **"What is the most important information I should know about SOLIRIS?"**

Before you receive SOLIRIS, 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 SOLIRIS will harm your unborn baby
- are breastfeeding or plan to breastfeed. It is not known if SOLIRIS passes into your breast milk

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

It is important that you:

- have all recommended vaccinations before you start SOLIRIS
- receive 2 weeks of antibiotics if you immediately start SOLIRIS
- stay up-to-date with all recommended vaccinations during treatment with SOLIRIS

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.

Please see accompanying full Prescribing Information and Medication Guide for Soliris, including boxed WARNING regarding serious meningococcal infections.

SOLIRIS®
(eculizumab)
Injection for Intravenous Use

Important Safety Information for Soliris (continued)

MONITORING DISEASE AFTER STOPPING SOLIRIS

If you have PNH, your doctor will need to monitor you closely for at least 8 weeks after stopping SOLIRIS. Stopping treatment with SOLIRIS 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
- drop in your platelet counts
- confusion
- kidney problems
- blood clots
- difficulty breathing
- chest pain

What are the possible side effects of SOLIRIS?

SOLIRIS can cause serious side effects including:

- See **"What is the most important information I should know about SOLIRIS?"**
- **Serious allergic reactions.** Serious allergic reactions can happen during your SOLIRIS infusion. Tell your doctor or nurse right away if you get any of these symptoms during your SOLIRIS infusion:
  1. chest pain
  2. trouble breathing or shortness of breath
  3. swelling of your face, tongue, or throat
  4. feel faint or pass out

If you have an allergic reaction to SOLIRIS, your doctor may need to infuse SOLIRIS more slowly, or stop SOLIRIS. See "How will I receive SOLIRIS?" in the Medication Guide.

The most common side effects in people with PNH treated with SOLIRIS include:

- headache
- pain or swelling of your nose or throat (nasopharyngitis)
- back pain
- nausea

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 SOLIRIS. 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.

ONESOURCE™
Personalized Patient Support from Alexion

Call 1.888.765.4747 or visit Soliris.net/patients/one-source.

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Please see accompanying full Prescribing Information and Medication Guide for Soliris, including boxed WARNING regarding serious meningococcal infections.

SOLIRIS®
(eculizumab)
Injection for Intravenous Use

US/SOL-P/0024

Indication and Select Important Safety Information for ULTOMIRIS

INDICATION

What is ULTOMIRIS® (ravulizumab-cwvz)?

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.

SELECT 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

What you should know about ULTOMIRIS

What is ULTOMIRIS?

- ULTOMIRIS is a complement inhibitor indicated for treatment of adult patients with PNH
- ULTOMIRIS is called a long-acting medicine because it remains effective in your body for 8 weeks
- With every-8-week dosing, ULTOMIRIS only needs to be infused 6-7 times a year
- In the largest PNH clinical trial program to date, ULTOMIRIS was studied in patients with PNH, including those new to treatment and those previously treated with eculizumab

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

Ask your doctor about starting or switching to ULTOMIRIS.

To learn more, visit www.ULTOMIRIS.com

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

Please see Important Safety Information on pages 26-29.

ULTOMIRIS® (ravulizumab-cwvz) injection for intravenous use 300 mg/30 mL vial

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Indication and Important Safety Information for ULTOMIRIS

INDICATION

What is ULTOMIRIS® (ravulizumab-cwvz)?

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

Important Safety Information for ULTOMIRIS (continued)

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 breast feed during treatment and for 8 months after your final dose of ULTOMIRIS.

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

Important Safety Information for ULTOMIRIS (continued)

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
  - blood clots
  - shortness of breath
  - trouble swallowing
  - erectile dysfunction (ED) in males
- If you miss an ULTOMIRIS infusion, call your doctor right away.

Important Safety Information for ULTOMIRIS (continued)

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.

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

US/SOL-P/0024

Glossary

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 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 the cells in your blood: red blood cells, white blood cells, and platelets.

Complement—Also known as complement cascade; in healthy individuals, 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 (ED)—A condition found in men that affects their ability to achieve an erection.

Fatigue—Tiredness, trouble concentrating, and weakness to the point where even normal, everyday activities become a struggle. In PNH, fatigue is often out of proportion to the amount of anemia, as measured by hemoglobin, because it is affected by hemolysis.

Hemolysis—When red blood cells burst. Hemolysis is the main cause of the major health problems in PNH.

Glossary (continued)

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 burst (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 protein 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.

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Notes

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Select Important Safety Information for Soliris

SELECT IMPORTANT SAFETY INFORMATION

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

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

- **SOLIRIS 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 SOLIRIS if you have not already had this vaccine.
2. If your doctor decided that urgent treatment with SOLIRIS is needed, you should receive meningococcal vaccination as soon as possible.
3. If you have not been vaccinated and SOLIRIS 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 SOLIRIS. 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, confusion, muscle aches with flu-like symptoms, eyes sensitive to light.

Please see accompanying full Prescribing Information and Medication Guide for Soliris, including boxed WARNING regarding serious meningococcal infections.

SOLIRIS® (eculizumab) Injection for Intravenous Use

Select Important Safety Information for ULTOMIRIS

SELECT 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 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

Notes

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Notes

Notes

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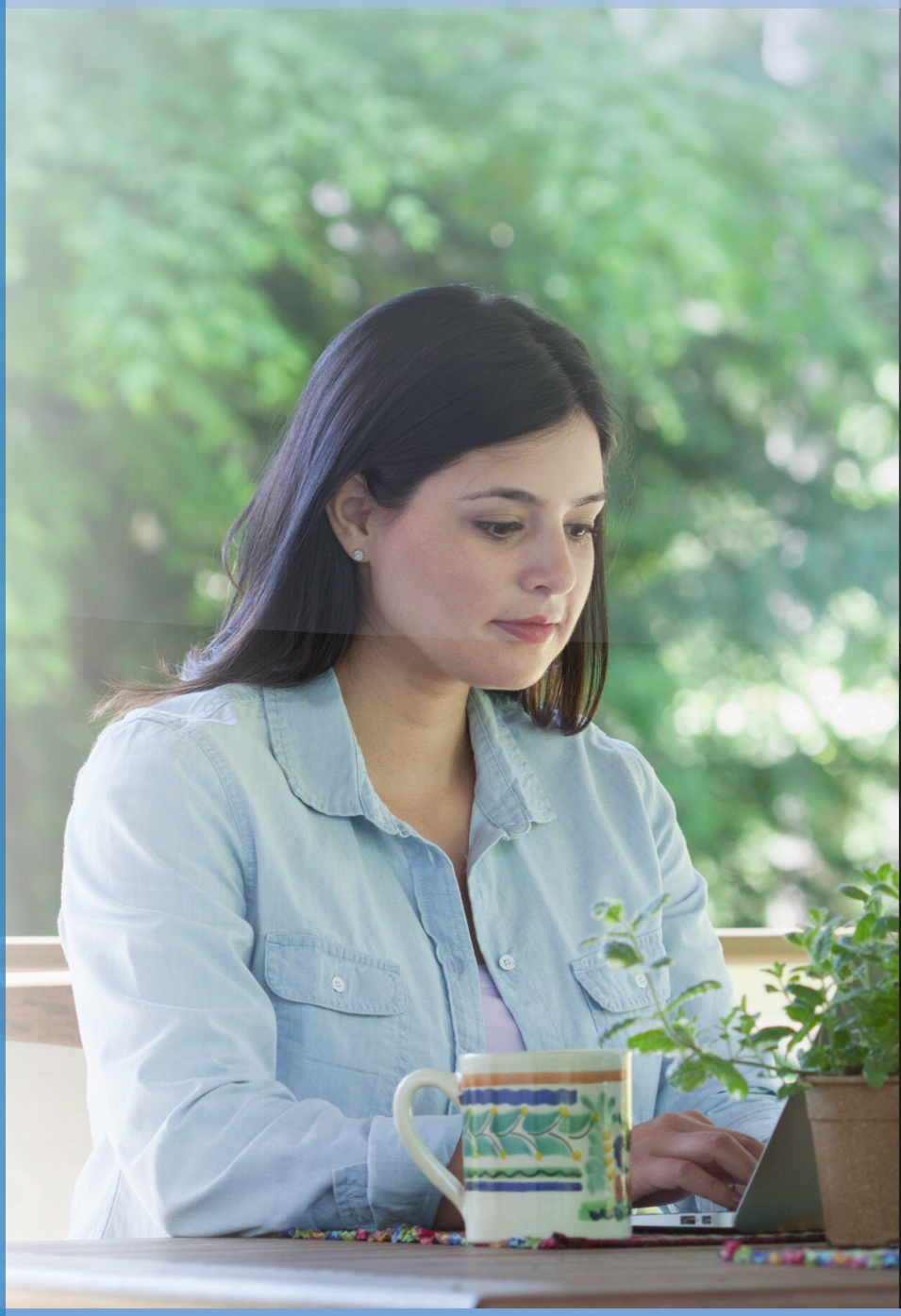
You and your physician can talk to a OneSource™ Alexion Case Manager for free to learn more about your disease, resources that are available, and support regarding financial information or coverage.

Call 1.888.765.4747 and get the conversation going.



ALEXION®

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SOLIRIS safely and effectively. See full prescribing information for SOLIRIS.

SOLIRIS® (eculizumab) injection, for intravenous use
Initial U.S. Approval: 2007

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS
See full prescribing information for complete boxed warning

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris and may become rapidly life-threatening or fatal if not recognized and treated early (5.1).

- **Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies (5.1).**
- **Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of Soliris, unless the risks of delaying Soliris therapy outweigh the risks 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 infections. Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.**

Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS, prescribers must enroll in the program (5.1).

RECENT MAJOR CHANGES

Indications and Usage (1.4)	06/2019
Dosage and Administration (2.4, 2.5)	06/2019
Dosage and Administration (2.5, 2.6, 2.7)	07/2018
Warnings and Precautions (5.1, 5.2)	07/2018

INDICATIONS AND USAGE

Soliris is a complement inhibitor indicated for:

- The treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis (1.1).
- The treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (1.2).

  Limitation of Use
  Soliris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).
- The treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AchR) antibody positive (1.3).
- The treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive (1.4).

DOSAGE AND ADMINISTRATION

For intravenous infusion only
PNH Dosage Regimen: (2.2)
aHUS Dosage Regimen: (2.3)
gMG and NMOSD Dosage Regimen: (2.4)

DOSAGE FORMS AND STRENGTHS

Injection: 300 mg/30 mL (10 mg/mL) in a single-dose vial (3).

CONTRAINDICATIONS

Soliris is contraindicated in:

- Patients with unresolved serious *Neisseria meningitidis* infection (4).
- Patients who are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying Soliris treatment outweigh the risks of developing a meningococcal infection (5.1).

WARNINGS AND PRECAUTIONS

- Discontinue Soliris in patients who are being treated for serious meningococcal infections (5.1).
- Use caution when administering Soliris to patients with any other systemic infection (5.2).

ADVERSE REACTIONS

The most frequently reported adverse reactions in the PNH randomized trial (≥10% overall and greater than placebo) are: headache, nasopharyngitis, back pain, and nausea (6.1).

The most frequently reported adverse reactions in aHUS single arm prospective trials (≥20%) are: headache, diarrhea, hypertension, upper respiratory infection, abdominal pain, vomiting, nasopharyngitis, anemia, cough, peripheral edema, nausea, urinary tract infections, pyrexia (6.1).

The most frequently reported adverse reaction in the gMG placebo-controlled clinical trial (≥10%) is: musculoskeletal pain (6.1).

The most frequently reported adverse reactions in the NMOSD placebo-controlled trial (≥10%) are: upper respiratory infection, nasopharyngitis, diarrhea, back pain, dizziness, influenza, arthralgia, pharyngitis, and contusion (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: 06/2019

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early [*see Warnings and Precautions (5.1)*].

- **Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.**
- **Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of Soliris, unless the risks of delaying Soliris therapy outweigh 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 infections. Monitor patients for early signs of meningococcal infections and evaluate immediately if infection is suspected.**

Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS, prescribers must enroll in the program [*see Warnings and Precautions (5.1)*]. Enrollment in the Soliris REMS program and additional information are available by telephone: 1-888-SOLIRIS (1-888-765-4747) or at www.solirisrems.com.

1 INDICATIONS AND USAGE

1.1 Paroxysmal Nocturnal Hemoglobinuria (PNH)

Soliris is indicated for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis.

1.2 Atypical Hemolytic Uremic Syndrome (aHUS)

Soliris is indicated for the treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy.

Limitation of Use
Soliris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

1.3 Generalized Myasthenia Gravis (gMG)

Soliris is indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AchR) antibody positive.

1.4 Neuromyelitis Optica Spectrum Disorder (NMOSD)

Soliris is indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Vaccination and Prophylaxis

Vaccinate patients according to current ACIP guidelines to reduce the risk of serious infection [*see Warnings and Precautions (5.1 and 5.2)*].

Provide two weeks of antibacterial drug prophylaxis to patients if Soliris must be initiated immediately and vaccines are administered less than two weeks before starting Soliris therapy.

Healthcare professionals who prescribe Soliris must enroll in the Soliris REMS [*see Warnings and Precautions (5.1)*].

2.2 Recommended Dosage Regimen – PNH

For patients 18 years of age and older, Soliris therapy consists of:

- 600 mg weekly for the first 4 weeks, followed by
- 900 mg for the fifth dose 1 week later, then

- 900 mg every 2 weeks thereafter.

Administer Soliris at the recommended dosage regimen time points, or within two days of these time points *[see Warnings and Precautions (5.4)]*.

2.3 Recommended Dosage Regimen – aHUS

For patients 18 years of age and older, Soliris therapy consists of:

- 900 mg weekly for the first 4 weeks, followed by
- 1200 mg for the fifth dose 1 week later, then
- 1200 mg every 2 weeks thereafter.

For patients less than 18 years of age, administer Soliris based upon body weight, according to the following schedule (Table 1):

Table 1: Dosing Recommendations in aHUS Patients Less Than 18 Years of Age

Patient Body Weight	Induction	Maintenance
40 kg and over	900 mg weekly x 4 doses	1200 mg at week 5; then 1200 mg every 2 weeks
30 kg to less than 40 kg	600 mg weekly x 2 doses	900 mg at week 3; then 900 mg every 2 weeks
20 kg to less than 30 kg	600 mg weekly x 2 doses	600 mg at week 3; then 600 mg every 2 weeks
10 kg to less than 20 kg	600 mg weekly x 1 dose	300 mg at week 2; then 300 mg every 2 weeks
5 kg to less than 10 kg	300 mg weekly x 1 dose	300 mg at week 2; then 300 mg every 3 weeks

Administer Soliris at the recommended dosage regimen time points, or within two days of these time points.

2.4 Recommended Dosage Regimen – gMG and NMOSD

For adult patients with generalized myasthenia gravis or neuromyelitis optica spectrum disorder, Soliris therapy consists of:

- 900 mg weekly for the first 4 weeks, followed by
- 1200 mg for the fifth dose 1 week later, then
- 1200 mg every 2 weeks thereafter.

Administer Soliris at the recommended dosage regimen time points, or within two days of these time points.

2.5 Dose Adjustment in Case of Plasmapheresis, Plasma Exchange, or Fresh Frozen Plasma Infusion

For adult and pediatric patients with aHUS, and adult patients with gMG or NMOSD, supplemental dosing of Soliris is required in the setting of concomitant plasmapheresis or plasma exchange, or fresh frozen plasma infusion (PE/PI) (Table 2).

Table 2: Supplemental Dose of Soliris after PE/PI

Type of Plasma Intervention	Most Recent Soliris Dose	Supplemental Soliris Dose With Each Plasma Intervention	Timing of Supplemental Soliris Dose
Plasmapheresis or plasma exchange	300 mg	300 mg per each plasmapheresis or plasma exchange session	Within 60 minutes after each plasmapheresis or plasma exchange
	≥600 mg	600 mg per each plasmapheresis or plasma exchange session	
Fresh frozen plasma infusion	≥300 mg	300 mg per infusion of fresh frozen plasma	60 minutes prior to each infusion of fresh frozen plasma

2.6 Preparation

Dilute Soliris to a final admixture concentration of 5 mg/mL using the following steps:

- Withdraw the required amount of Soliris from the vial into a sterile syringe.
- Transfer the recommended dose to an infusion bag.
- Dilute Soliris to a final concentration of 5 mg/mL by adding the appropriate amount (equal volume of diluent to drug volume) of 0.9% Sodium Chloride Injection, USP; 0.45% Sodium Chloride Injection, USP; 5% Dextrose in Water Injection, USP; or Ringer's Injection, USP to the infusion bag.

The final admixed Soliris 5 mg/mL infusion volume is 60 mL for 300 mg doses, 120 mL for 600 mg doses, 180 mL for 900 mg doses or 240 mL for 1200 mg doses (Table 3).

Table 3: Preparation and Reconstitution of Soliris

Soliris Dose	Diluent Volume	Final Volume
300 mg	30 mL	60 mL
600 mg	60 mL	120 mL
900 mg	90 mL	180 mL
1200 mg	120 mL	240 mL

Gently invert the infusion bag containing the diluted Soliris solution to ensure thorough mixing of the product and diluent. Discard any unused portion left in a vial, as the product contains no preservatives.

Prior to administration, the admixture should be allowed to adjust to room temperature [18°-25° C, 64°-77° F]. The admixture must not be heated 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.

2.7 Administration

Only administer as an intravenous infusion.

Do not administer as an intravenous push or bolus injection.

Administer the Soliris admixture by intravenous infusion over 35 minutes in adults and 1 to 4 hours in pediatric patients via gravity feed, a syringe-type pump, or an infusion pump. Admixed solutions of Soliris are stable for 24 h at 2°-8° C (36°-46° F) and at room temperature.

If an adverse reaction occurs during the administration of Soliris, the infusion may be slowed or stopped at the discretion of the physician. If the infusion is slowed, the total infusion time should not exceed two hours in adults. 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, colorless solution in a single-dose vial.

4 CONTRAINDICATIONS

Soliris is contraindicated in:

- Patients with unresolved serious *Neisseria meningitidis* infection [*see Warnings and Precautions (5.1)*].
- Patients who are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying Soliris treatment outweigh the risks of developing a meningococcal infection [*see Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Serious Meningococcal Infections

Risk and Prevention

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. The use of Soliris increases a patient's susceptibility to serious meningococcal infections (septicemia and/or meningitis). Soliris is associated with an approximate 2,000-fold increased risk of meningococcal disease in comparison to the general U.S. population annual rate (0.14 per 100,000 population in 2015).

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 Soliris therapy.

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

In prospective clinical studies, 75/100 patients with aHUS were treated with Soliris less than 2 weeks after meningococcal vaccination and 64 of these 75 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 Soliris have not been established.

Vaccination reduces, but does not eliminate, the risk of meningococcal infections. In clinical studies, 2 out of 196 PNH patients developed serious meningococcal infections while receiving treatment with Soliris; both had been vaccinated [*see Adverse Reactions (6.1)*]. In clinical studies among non-PNH patients, meningococcal meningitis occurred in one unvaccinated patient. In addition, 3 out of 130 previously vaccinated patients with aHUS developed meningococcal infections while receiving treatment with Soliris [*see Adverse Reactions (6.1)*].

Closely monitor patients for early signs and symptoms of meningococcal infection and evaluate patients immediately if an infection is suspected. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early. Discontinue Soliris in patients who are undergoing treatment for serious meningococcal infections.

REMS

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

Prescribers must counsel patients about the risk of meningococcal infection, provide the patients with the REMS educational materials, and ensure patients are vaccinated with meningococcal vaccine(s).

Enrollment in the Soliris REMS program and additional information are available by telephone: 1-888-SOLIRIS (1-888-765-4747) or at www.solirisrems.com.

5.2 Other Infections

Serious infections with *Neisseria* species (other than *N. meningitidis*), including disseminated gonococcal infections, have been reported.

Soliris blocks terminal complement activation; therefore patients may have increased susceptibility to infections, especially with encapsulated bacteria. Additionally, *Aspergillus* infections have occurred in immunocompromised and neutropenic patients. Children treated with Soliris may be at increased risk of developing serious infections due to *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib). Administer vaccinations for the prevention of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) infections according to ACIP guidelines. Use caution when administering Soliris to patients with any systemic infection [*see Warnings and Precautions (5.1)*].

5.3 Monitoring Disease Manifestations after Soliris Discontinuation

Treatment Discontinuation for PNH

Monitor patients after discontinuing Soliris for at least 8 weeks to detect hemolysis.

Treatment Discontinuation for aHUS

After discontinuing Soliris, monitor patients with aHUS for signs and symptoms of thrombotic microangiopathy (TMA) complications for at least 12 weeks. In aHUS clinical trials, 18 patients (5 in the prospective studies) discontinued Soliris treatment. TMA complications occurred following a missed dose in 5 patients, and Soliris was reinitiated in 4 of these 5 patients.

Clinical signs and symptoms of TMA include changes in mental status, seizures, angina, dyspnea, or thrombosis. In addition, the following changes in laboratory parameters may identify a TMA complication: occurrence of two, or repeated measurement of any one of the following: a decrease in platelet count by 25% or more compared to baseline or the peak platelet count during Soliris treatment; an increase in serum creatinine by 25% or more compared to baseline or nadir during Soliris treatment; or, an increase in serum LDH by 25% or more over baseline or nadir during Soliris treatment.

If TMA complications occur after Soliris discontinuation, consider reinstitution of Soliris treatment, plasma therapy [plasmapheresis, plasma exchange, or fresh frozen plasma infusion (PE/PI)], or appropriate organ-specific supportive measures.

5.4 Thrombosis Prevention and Management

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

5.5 Infusion Reactions

Administration of Soliris may result in infusion reactions, including anaphylaxis or other hypersensitivity reactions. In clinical trials, no patients experienced an infusion reaction which required discontinuation of Soliris. Interrupt Soliris infusion and institute appropriate supportive measures if signs of cardiovascular instability or respiratory compromise occur.

6 ADVERSE REACTIONS

The following serious 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 Disease Manifestations after Soliris Discontinuation [*see Warnings and Precautions (5.3)*]
- Thrombosis Prevention and Management [*see Warnings and Precautions (5.4)*]
- 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.

Meningococcal infections are the most important adverse reactions experienced by patients receiving Soliris. In PNH clinical studies, two patients experienced meningococcal sepsis. Both patients had previously received a meningococcal vaccine. In clinical studies among patients without PNH, meningococcal meningitis occurred in one unvaccinated patient. Meningococcal sepsis occurred in one previously vaccinated patient enrolled in the retrospective aHUS study during the post-study follow-up period [*see Warnings and Precautions (5.1)*].

PNH

The data described below reflect exposure to Soliris in 196 adult patients with PNH, age 18-85, of whom 55% were female. All had signs or symptoms of intravascular hemolysis. Soliris was studied in a placebo-controlled clinical study (PNH Study 1, in which 43 patients received Soliris and 44, placebo); a single arm clinical study (PNH Study 2); and a long term extension study (E05-001). 182 patients were exposed for greater than one year. All patients received the recommended Soliris dose regimen.

Table 4 summarizes the adverse reactions that occurred at a numerically higher rate in the Soliris group than the placebo group and at a rate of 5% or more among patients treated with Soliris.

Table 4: Adverse Reactions Reported in 5% or More of Soliris Treated Patients with PNH and Greater than Placebo in the Controlled Clinical Study

Reaction	Soliris (N=43) N (%)	Placebo (N=44) N (%)
Headache	19 (44)	12 (27)
Nasopharyngitis	10 (23)	8 (18)
Back pain	8 (19)	4 (9)
Nausea	7 (16)	5 (11)
Fatigue	5 (12)	1 (2)
Cough	5 (12)	4 (9)
Herpes simplex infections	3 (7)	0
Sinusitis	3 (7)	0
Respiratory tract infection	3 (7)	1 (2)
Constipation	3 (7)	2 (5)
Myalgia	3 (7)	1 (2)
Pain in extremity	3 (7)	1 (2)
Influenza-like illness	2 (5)	1 (2)

In the placebo-controlled clinical study, serious adverse reactions occurred among 4 (9%) patients receiving Soliris and 9 (21%) patients receiving placebo. The serious reactions included infections and progression of PNH. No deaths occurred in the study and no patients receiving Soliris experienced a thrombotic event; one thrombotic event occurred in a patient receiving placebo.

Among 193 patients with PNH treated with Soliris in the single arm, clinical study or the follow-up study, the adverse reactions were similar to those reported in the placebo-controlled clinical study. Serious adverse reactions occurred among 16% of the patients in these studies. The most common serious adverse reactions were: viral infection (2%), headache (2%), anemia (2%), and pyrexia (2%).

aHUS

The safety of Soliris therapy in patients with aHUS was evaluated in four prospective, single-arm studies, three in adult and adolescent patients (Studies C08-002A/B, C08-003A/B, and C10-004), one in pediatric and adolescent patients (Study C10-003), and one retrospective study (Study C09-001r).

The data described below were derived from 78 adult and adolescent patients with aHUS in Studies C08-002A/B, C08-003A/B and C10-004. All patients received the recommended dosage of Soliris. Median exposure was 67 weeks (range: 2-145 weeks). Table 5 summarizes all adverse events reported in at least 10% of patients in Studies C08-002A/B, C08-003A/B and C10-004 combined.

Table 5: Per Patient Incidence of Adverse Events in 10% or More Adult and Adolescent Patients Enrolled in Studies C08-002A/B, C08-003A/B and C10-004 Separately and in Total

	Number (%) of Patients			
	C08-002A/B (N=17)	C08-003A/B (N=20)	C10-004 (N=41)	Total (N=78)
Vascular Disorders				
Hypertension[a]	10 (59)	9 (45)	7 (17)	26 (33)
Hypotension	2 (12)	4 (20)	7 (17)	13 (17)
Infections and Infestations				
Bronchitis	3 (18)	2 (10)	4 (10)	9 (12)
Nasopharyngitis	3 (18)	11 (55)	7 (17)	21 (27)
Gastroenteritis	3 (18)	4 (20)	2 (5)	9 (12)
Upper respiratory tract infection	5 (29)	8 (40)	2 (5)	15 (19)
Urinary tract infection	6 (35)	3 (15)	8 (20)	17 (22)
Gastrointestinal Disorders				
Diarrhea	8 (47)	8 (40)	12 (32)	29 (37)
Vomiting	8 (47)	9 (45)	6 (15)	23 (30)
Nausea	5 (29)	8 (40)	5 (12)	18 (23)
Abdominal pain	3 (18)	6 (30)	6 (15)	15 (19)
Nervous System Disorders				
Headache	7 (41)	10 (50)	15 (37)	32 (41)
Blood and Lymphatic System Disorders				
Anemia	6 (35)	7 (35)	7 (17)	20 (26)
Leukopenia	4 (24)	3 (15)	5 (12)	12 (15)
Psychiatric Disorders				
Insomnia	4 (24)	2 (10)	5 (12)	11 (14)
Renal and Urinary Disorders				
Renal Impairment	5 (29)	3 (15)	6 (15)	14 (18)
Proteinuria	2 (12)	1 (5)	5 (12)	8 (10)
Respiratory, Thoracic and Mediastinal Disorders				
Cough	4 (24)	6 (30)	8 (20)	18 (23)
General Disorders and Administration Site Conditions				
Fatigue	3 (18)	4 (20)	3 (7)	10 (13)
Peripheral edema	5 (29)	4 (20)	9 (22)	18 (23)
Pyrexia	4 (24)	5 (25)	7 (17)	16 (21)
Asthenia	3 (18)	4 (20)	6 (15)	13 (17)
Eye Disorder	5 (29)	2 (10)	8 (20)	15 (19)
Metabolism and Nutrition Disorders				
Hypokalemia	3 (18)	2 (10)	4 (10)	9 (12)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	1 (6)	6 (30)	1 (20)	8 (10)
Skin and Subcutaneous Tissue Disorders				
Rash	2 (12)	3 (15)	6 (15)	11 (14)
Pruritus	1 (6)	3 (15)	4 (10)	8 (10)
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	1 (6)	2 (10)	7 (17)	10 (13)
Back pain	3 (18)	3 (15)	2 (5)	8 (10)

[a] includes the preferred terms hypertension, accelerated hypertension, and malignant hypertension.

In Studies C08-002A/B, C08-003A/B and C10-004 combined, 60% (47/78) of patients experienced a serious adverse event (SAE). The most commonly reported SAEs were infections (24%), hypertension (5%), chronic renal failure (5%), and renal impairment (5%). Five patients discontinued Soliris due to adverse events; three due to worsening renal function, one due to new diagnosis of Systemic Lupus Erythematosus, and one due to meningococcal meningitis.

Study C10-003 included 22 pediatric and adolescent patients, of which 18 patients were less than 12 years of age. All patients received the recommended dosage of Soliris. Median exposure was 44 weeks (range: 1 dose-87 weeks).

Table 6 summarizes all adverse events reported in at least 10% of patients enrolled in Study C10-003.

Table 6: Per Patient Incidence of Adverse Reactions in 10% or More Patients Enrolled in Study C10-003

	1 month to <12 yrs (N=18)	Total (N=22)
Eye Disorders	3 (17)	3 (14)
Gastrointestinal Disorders		
Abdominal pain	6 (33)	7 (32)
Diarrhea	5 (28)	7 (32)
Vomiting	4 (22)	6 (27)
Dyspepsia	0	3 (14)
General Disorders and Administration Site Conditions		
Pyrexia	9 (50)	11 (50)
Infections and Infestations		
Upper respiratory tract infection	5 (28)	7 (32)
Nasopharyngitis	3 (17)	6 (27)
Rhinitis	4 (22)	4 (18)
Urinary Tract infection	3 (17)	4 (18)
Catheter site infection	3 (17)	3 (14)
Musculoskeletal and Connective Tissue Disorders		
Muscle spasms	2 (11)	3 (14)
Nervous System Disorders		
Headache	3 (17)	4 (18)
Renal and Urinary Disorders	3 (17)	4 (18)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	7 (39)	8 (36)
Oropharyngeal pain	1 (6)	3 (14)
Skin and Subcutaneous Tissue Disorders		
Rash	4 (22)	4 (18)
Vascular Disorders		
Hypertension	4 (22)	4 (18)

In Study C10-003, 59% (13/22) of patients experienced a serious adverse event (SAE). The most commonly reported SAEs were hypertension (9%), viral gastroenteritis (9%), pyrexia (9%), and upper respiratory infection (9%). One patient discontinued Soliris due to an adverse event (severe agitation).

Analysis of retrospectively collected adverse event data from pediatric and adult patients enrolled in Study C09-001r (N=30) revealed a safety profile that was similar to that which was observed in the two prospective studies. Study C09-001r included 19 pediatric patients less than 18 years of age. Overall, the safety of Soliris in pediatric patients with aHUS enrolled in Study C09-001r appeared similar to that observed in adult patients. The most common (≥15%) adverse events occurring in pediatric patients are presented in Table 7.

Table 7: Adverse Reactions Occurring in at Least 15% of Patients Less than 18 Years of Age Enrolled in Study C09-001r

	Number (%) of Patients			
	<2 yrs (N=5)	2 to <12 yrs (N=10)	12 to <18 yrs (N=4)	Total (N=19)
General Disorders and Administration Site Conditions				
Pyrexia	4 (80)	4 (40)	1 (25)	9 (47)
Gastrointestinal Disorders				
Diarrhea	1 (20)	4 (40)	1 (25)	6 (32)
Vomiting	2 (40)	1 (10)	1 (25)	4 (21)
Infections and Infestations				
Upper respiratory tract infection[a]	2 (40)	3 (30)	1 (25)	6 (32)
Respiratory, Thoracic and Mediastinal Disorders				
Cough	3 (60)	2 (20)	0 (0)	5 (26)
Nasal congestion	2 (40)	2 (20)	0 (0)	4 (21)
Cardiac Disorders				
Tachycardia	2 (40)	2 (20)	0 (0)	4 (21)

[a] includes the preferred terms upper respiratory tract infection and nasopharyngitis.

Generalized Myasthenia Gravis (gMG)

In a 26-week placebo-controlled trial evaluating the effect of Soliris for the treatment of gMG (gMG Study 1), 62 patients received Soliris at the recommended dosage regimen and 63 patients received placebo [*see Clinical Studies (14.3)*]. Patients were 19 to 79 years of age, and 66% were female. Table 8 displays the most common adverse reactions from gMG Study 1 that occurred in ≥5% of Soliris-treated patients and at a greater frequency than on placebo.

Table 8: Adverse Reactions Reported in 5% or More of Soliris-Treated Patients in gMG Study 1 and at a Greater Frequency than in Placebo-Treated Patients

	Soliris (N=62) N (%)	Placebo (N=63) N (%)
Gastrointestinal Disorders		
Abdominal pain	5 (8)	3 (5)
General Disorders and Administration Site Conditions		
Peripheral edema	5 (8)	3 (5)
Pyrexia	4 (7)	2 (3)
Infections and Infestations		
Herpes simplex virus infections	5 (8)	1 (2)
Injury, Poisoning, and Procedural Complications		
Contusion	5 (8)	2 (3)
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain	9 (15)	5 (8)

The most common adverse reactions (≥10%) that occurred in Soliris-treated patients in the long-term extension to gMG Study 1, Study ECU-MG-302, and that are not included in Table 8 were headache (26%), nasopharyngitis (24%), diarrhea (15%), arthralgia (12%), upper respiratory tract infection (11%), and nausea (10%).

Neuromyelitis Optica Spectrum Disorder (NMOSD)

In a placebo-controlled trial evaluating the effect of Soliris for the treatment of NMOSD (NMOSD Study 1), 96 patients received Soliris at the recommended dosage regimen and 47 patients received placebo [*see Clinical Studies (14.4)*]. Patients were 19 to 75 years of age (mean 44 years of age), and 91% were female. Table 9 displays the most common adverse reactions from NMOSD Study 1 that occurred in ≥5% of Soliris-treated patients and at a greater frequency than on placebo.

Table 9: Adverse Reactions Reported in 5% or More of Soliris-Treated Patients in NMOSD Study 1 and at a Greater Frequency than in Placebo-Treated Patients

	Soliris (N=96) N (%)	Placebo (N=47) N (%)
Events/Patients	1295/88	617/45
Blood and lymphatic system disorders		
Leukopenia	5 (5)	1 (2)
Lymphopenia	5 (5)	0 (0)
Eye disorders		
Cataract	6 (6)	2 (4)
Gastrointestinal disorders		
Diarrhea	15 (16)	7 (15)
Constipation	9 (9)	3 (6)
General disorders and administration site conditions		
Asthenia	5 (5)	1 (2)
Infections and infestations		
Upper respiratory tract infection	28 (29)	6 (13)
Nasopharyngitis	20 (21)	9 (19)
Influenza	11 (11)	2 (4)
Pharyngitis	10 (10)	3 (6)
Bronchitis	9 (9)	3 (6)
Conjunctivitis	9 (9)	4 (9)
Cystitis	8 (8)	1 (2)
Hordeolum	7 (7)	0 (0)
Sinusitis	6 (6)	0 (0)
Cellulitis	5 (5)	1 (2)
Injury, poisoning and procedural complications		
Contusion	10 (10)	2 (4)
Metabolism and nutrition disorders		
Decreased appetite	5 (5)	1 (2)
Musculoskeletal and connective tissue disorders		
Back pain	14 (15)	6 (13)
Arthralgia	11 (11)	5 (11)
Musculoskeletal pain	6 (6)	0 (0)
Muscle spasms	5 (5)	2 (4)
Nervous system disorders		
Dizziness	14 (15)	6 (13)
Paraesthesia	8 (8)	3 (6)
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain	7 (7)	2 (4)
Skin and subcutaneous tissue disorders		
Alopecia	5 (5)	2 (4)

6.2 Immunogenicity

As with all proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) 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 to eculizumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

The immunogenicity of Soliris has been evaluated using two different immunoassays for the detection of anti-eculizumab antibodies: a direct enzyme-linked immunosorbent assay (ELISA) using the Fab fragment of eculizumab as target was used for the PNH indication; and an electro-chemiluminescence (ECL) bridging assay using the eculizumab whole molecule as target was used for the aHUS, gMG, and NMOSD indications, as well as for additional patients with PNH. In the PNH population, antibodies to Soliris were detected in 3/196 (2%) patients using the ELISA assay and in 5/161 (3%) patients using the ECL assay. In the aHUS population, antibodies to Soliris were detected in 3/100 (3%) patients using the ECL assay. None of the 62 patients with gMG had antibodies to Soliris detected following the 26-week active treatment. Two of the 96 (2%) Soliris-treated patients with NMOSD had antibodies to Soliris detected during the entire treatment period.

An ECL based neutralizing assay with a low sensitivity of 2 mcg/mL was performed to detect neutralizing antibodies for the 5 patients with PNH, the 3 patients with aHUS, and the 2 patients with NMOSD with anti-eculizumab antibody positive samples using the ECL assay. Two of 161 patients with PNH (1.2%) and 1 of 100 patients with aHUS (1%), and none of the 96 patients with NMOSD had low positive values for neutralizing antibodies.

No apparent correlation of antibody development to clinical response was observed.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Soliris. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Soliris exposure.

Fatal or serious infections: *Neisseria gonorrhoeae, Neisseria meningitidis, Neisseria sicca/subflava, Neisseria spp* unspecified

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited data on outcomes of pregnancies that have occurred following Soliris use in pregnant women have not identified a concern for specific adverse developmental outcomes (*see Data*). There are risks to the mother and fetus associated with untreated paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS) in pregnancy (*see Clinical Considerations*). Animal studies using a mouse analogue of the Soliris molecule (murine anti-C5 antibody) showed increased rates of developmental abnormalities and an increased rate of dead and moribund offspring at doses 2-8 times the human dose (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or fetal/neonatal risk

PNH in pregnancy is associated with adverse maternal outcomes, including worsening cytopenias, thrombotic events, infections, bleeding, miscarriages and increased maternal mortality, and adverse fetal outcomes, including fetal death and premature delivery.

aHUS in pregnancy is associated with adverse maternal outcomes, including pre-eclampsia and preterm delivery, and adverse fetal/neonatal outcomes, including intrauterine growth restriction (IUGR), fetal death and low birth weight.

Data

Human Data

A pooled analysis of prospectively (50.3%) and retrospectively (49.7%) collected data in more than 300 pregnant women with live births following exposure to Soliris have not suggested safety concerns. However, these data cannot definitively exclude any drug-associated risk during pregnancy, because of the limited sample size.

Animal Data

Animal reproduction studies were conducted in mice using doses of a murine anti-C5 antibody that approximated 2-4 times (low dose) and 4-8 times (high dose) the recommended human Soliris dose, based on a body weight comparison. When animal exposure to the antibody occurred in the time period from before mating until early gestation, no decrease in fertility or reproductive performance was observed. When maternal exposure to the antibody occurred during organogenesis, two cases of retinal dysplasia and one case of umbilical hernia were observed among 230 offspring born to mothers exposed to the higher antibody dose; however, the exposure did not increase fetal loss or neonatal death. When maternal exposure to the antibody occurred in the time period from implantation through weaning, a

higher number of male offspring became moribund or died (1/25 controls, 2/25 low dose group, 5/25 high dose group). Surviving offspring had normal development and reproductive function.

8.2 Lactation

Risk Summary

Although limited published data does not report detectable levels of eculizumab in human milk, maternal IgG is known to be present in human milk. Available information is insufficient to inform the effect of eculizumab on the breastfed infant. There are no data on the effects of eculizumab on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Soliris and any potential adverse effects on the breastfed child from eculizumab or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of Soliris for the treatment of PNH, gMG, or NMOSD in pediatric patients have not been established.

The safety and effectiveness of Soliris for the treatment of aHUS have been established in pediatric patients. Use of Soliris in pediatric patients for this indication is supported by evidence from four adequate and well-controlled clinical studies assessing the safety and effectiveness of Soliris for the treatment of aHUS. The studies included a total of 47 pediatric patients (ages 2 months to 17 years). The safety and effectiveness of Soliris for the treatment of aHUS appear similar in pediatric and adult patients [*see Adverse Reactions (6.1), and Clinical Studies (14.2)*].

Administer vaccinations for the prevention of infection due to *Neisseria meningitidis, Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) according to ACIP guidelines [*see Warnings and Precautions (5.1, 5.2)*].

8.5 Geriatric Use

Fifty-one patients 65 years of age or older (15 with PNH, 4 with aHUS, 26 with gMG, and 6 with NMOSD) were treated with Soliris in clinical trials in the approved indications. Although there were no apparent age-related differences observed in these studies, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

11 DESCRIPTION

Eculizumab, a complement inhibitor, is a recombinant humanized monoclonal IgG2/4$_\kappa$ antibody produced by murine myeloma cell culture and purified by standard bioprocess technology. Eculizumab contains human constant regions from human IgG2 sequences and human IgG4 sequences and murine complementarity-determining regions grafted onto the human framework light- and heavy-chain variable regions. Eculizumab is composed of two 448 amino acid heavy chains and two 214 amino acid light chains and has a molecular weight of approximately 148 kDa.

Soliris (eculizumab) injection is a sterile, clear, colorless, preservative-free 10 mg/mL solution for intravenous infusion and is supplied in 30-mL single-dose vials. The product is formulated at pH 7 and each 30 mL vial contains 300 mg of eculizumab, polysorbate 80 (6.6 mg) (vegetable origin), sodium chloride (263.1 mg), sodium phosphate dibasic (53.4 mg), sodium phosphate monobasic (13.8 mg), and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Eculizumab, the active ingredient in Soliris, is a monoclonal antibody that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9.

Soliris inhibits terminal complement-mediated intravascular hemolysis in PNH patients and complement-mediated thrombotic microangiopathy (TMA) in patients with aHUS.

The precise mechanism by which eculizumab exerts its therapeutic effect in gMG patients is unknown, but is presumed to involve reduction of terminal complement complex C5b-9 deposition at the neuromuscular junction.

The precise mechanism by which eculizumab exerts its therapeutic effect in NMOSD is unknown, but is presumed to involve inhibition of aquaporin-4-antibody induced terminal complement C5b-9 deposition.

12.2 Pharmacodynamics

In the placebo-controlled clinical study (PNH Study 1), Soliris when administered as recommended reduced serum LDH levels from 2200 ± 1034 U/L (mean ± SD) at baseline to 700 ± 388 U/L by week one and maintained the effect through the end of the study at week 26 (327 ± 433 U/L) in patients with PNH. In the single arm clinical study (PNH Study 2), the effect was maintained through week 52 [*see Clinical Studies (14)*].

In patients with PNH, aHUS, gMG, and NMOSD, free C5 concentrations of < 0.5 mcg/mL was correlated with complete blockade of terminal complement activity.

12.3 Pharmacokinetics

Following intravenous maintenance doses of 900 mg once every 2 weeks in patients with PNH, the week 26 observed mean ± SD serum eculizumab maximum concentration (C_{max}) was 194 ± 76 mcg/mL and the trough concentration (C_{trough}) was 97 ± 60 mcg/mL. Following intravenous maintenance doses of 1200 mg once every 2 weeks in patients with aHUS, the week 26 observed mean ± SD C_{trough} was 242 ± 101 mcg/mL. Following intravenous maintenance doses of 1200 mg once every 2 weeks in patients with gMG, the week 26 observed mean ± SD C_{max} was 783 ± 288 mcg/mL and the C_{trough} was 341 ± 172 mcg/mL. Following intravenous maintenance doses of 1200 mg once every 2 weeks in patients with NMOSD, at week 24, the observed mean ± SD C_{max} was 877 ± 331 and the C_{trough} was 429 ± 188 mcg/mL.

Steady state was achieved 4 weeks after starting eculizumab treatment, with accumulation ratio of approximately 2-fold in all studied indications. Population pharmacokinetic analyses showed that eculizumab pharmacokinetics were dose-linear and time-independent over the 600 mg to 1200 mg dose range, with inter-individual variability of 21% to 38%.

Distribution

The eculizumab volume of distribution for a typical 70 kg patient was 5 L to 8 L.

Elimination

The half-life of eculizumab was approximately 270 h to 414 h.

Plasma exchange or infusion increased the clearance of eculizumab by approximately 250-fold and reduced the half-life to 1.26 h. Supplemental dosing is recommended when Soliris is administered to patients receiving plasma exchange or infusion [*see Dosage and Administration (2. 5)*].

Specific Populations

Age, Sex, and Race:

The pharmacokinetics of eculizumab were not affected by age (2 months to 85 years), sex, or race.

Renal Impairment:

Renal function did not affect the pharmacokinetics of eculizumab in PNH (creatinine clearance of 8 mL/min to 396 mL/min calculated using Cockcroft-Gault formula), aHUS (estimated glomerular filtration rate [eGFR] of 5 mL/min/1.73 m^2 to 105 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease [MDRD] formula), or gMG patients (eGFR of 44 mL/min/1.73 m^2 to 168 mL/min/1.73 m^2 using MDRD formula).

Drug Interactions

Intravenous immunoglobulin (IVIg) treatment may interfere with the endosomal neonatal Fc receptor (FcRn) recycling mechanism of monoclonal antibodies such as eculizumab and thereby decrease serum eculizumab concentrations. Drug interaction studies have not been conducted with eculizumab in patients treated with IVIg.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal carcinogenicity studies of eculizumab have not been conducted.

Genotoxicity studies have not been conducted with eculizumab.

Effects of eculizumab upon fertility have not been studied in animals. Intravenous injections of male and female mice with a murine anti-C5 antibody at up to 4-8 times the equivalent of the clinical dose of Soliris had no adverse effects on mating or fertility.

14 CLINICAL STUDIES

14.1 Paroxysmal Nocturnal Hemoglobinuria (PNH)

The safety and efficacy of Soliris in PNH patients with hemolysis were assessed in a randomized, double-blind, placebo-controlled 26 week study (PNH Study 1, NCT00122330); PNH patients were also treated with Soliris in a single arm 52 week study (PNH Study 2, NCT00122304) and in a long-term extension study (E05-001, NCT00122317). Patients received meningococcal vaccination prior to receipt of Soliris. In all studies, the dose of Soliris was 600 mg study drug every 7 ± 2 days for 4 weeks, followed by 900 mg 7 ± 2 days later, then 900 mg every 14 ± 2 days for the study duration. Soliris was administered as an intravenous infusion over 25 - 45 minutes.

PNH Study 1:

PNH patients with at least four transfusions in the prior 12 months, flow cytometric confirmation of at least 10% PNH cells and platelet counts of at least 100,000/microliter were randomized to either Soliris (n = 43) or placebo (n = 44). Prior to randomization, all patients underwent an initial observation period to confirm the need for RBC transfusion and to identify the hemoglobin concentration (the "set-point") which would define each patient's hemoglobin stabilization and transfusion outcomes. The hemoglobin set-point was less than or equal to 9 g/dL in patients with symptoms and was less than or equal to 7 g/dL in patients without symptoms. Endpoints related to hemolysis included the numbers of patients achieving hemoglobin stabilization, the number of RBC units transfused, fatigue, and health-related quality of life. To achieve a designation of hemoglobin stabilization, a patient had to maintain a hemoglobin concentration above the hemoglobin set-point and avoid any RBC transfusion for the entire 26 week period. Hemolysis was monitored mainly by the measurement of serum LDH levels, and the proportion of PNH RBCs was monitored by flow cytometry. Patients receiving anticoagulants and systemic corticosteroids at baseline continued these medications.

Major baseline characteristics were balanced (see Table 10).

Table 10: PNH Study 1 Patient Baseline Characteristics

Parameter	Study 1	
	Placebo (N=44)	Soliris (N=43)
Mean age (SD)	38 (13)	42 (16)
Gender - female (%)	29 (66)	23 (54)
History of aplastic anemia or myelodysplastic syndrome (%)	12 (27)	8 (19)
Patients with history of thrombosis (events)	8 (11)	9 (16)
Concomitant anticoagulants (%)	20 (46)	24 (56)
Concomitant steroids/immunosuppressant treatments (%)	16 (36)	14 (33)
Packed RBC units transfused per patient in previous 12 months (median (Q1,Q3))	17 (14, 25)	18 (12, 24)
Mean Hgb level (g/dL) at setpoint (SD)	8 (1)	8 (1)
Pre-treatment LDH levels (median, U/L)	2,234	2,032
Free hemoglobin at baseline (median, mg/dL)	46	41

Patients treated with Soliris had significantly reduced (p< 0.001) hemolysis resulting in improvements in anemia as indicated by increased hemoglobin stabilization and reduced need for RBC transfusions compared to placebo treated patients (see Table 11). These effects were seen among patients within each of the three pre-study RBC transfusion strata (4 - 14 units; 15 - 25 units; > 25 units). After 3 weeks of Soliris treatment, patients reported less fatigue and improved health-related quality of life. Because of the study sample size and duration, the effects of Soliris on thrombotic events could not be determined.

Table 11: PNH Study 1 Results

	Placebo (N=44)	Soliris (N=43)
Percentage of patients with stabilized hemoglobin levels	0	49
Packed RBC units transfused per patient (median)	10	0
(range)	(2 - 21)	(0 - 16)
Transfusion avoidance (%)	0	51
LDH levels at end of study (median, U/L)	2,167	239
Free hemoglobin at end of study (median, mg/dL)	62	5

PNH Study 2 and Extension Study:

PNH patients with at least one transfusion in the prior 24 months and at least 30,000 platelets/microliter received Soliris over a 52-week period. Concomitant medications included anti-thrombotic agents in 63% of the patients and systemic corticosteroids in 40% of the patients. Overall, 96 of the 97 enrolled patients completed the study (one patient died following a thrombotic event). A reduction in intravascular hemolysis as measured by serum LDH levels was sustained for the treatment period and resulted in a reduced need for RBC transfusion and less fatigue. 187 Soliris-treated PNH patients were enrolled in

a long term extension study. All patients sustained a reduction in intravascular hemolysis over a total Soliris exposure time ranging from 10 to 54 months. There were fewer thrombotic events with Soliris treatment than during the same period of time prior to treatment. However, the majority of patients received concomitant anticoagulants; the effects of anticoagulant withdrawal during Soliris therapy was not studied [*see Warnings and Precautions (5.4)*].

14.2 Atypical Hemolytic Uremic Syndrome (aHUS)

Five single-arm studies [four prospective: C08-002A/B (NCT00844545 and NCT00844844), C08-003A/B (NCT00838513 and NCT00844428), C10-003 (NCT01193348), and C10-004 (NCT01194973); and one retrospective: C09-001r (NCT01770951)] evaluated the safety and efficacy of Soliris for the treatment of aHUS. Patients with aHUS received meningococcal vaccination prior to receipt of Soliris or received prophylactic treatment with antibiotics until 2 weeks after vaccination. In all studies, the dose of Soliris in adult and adolescent patients was 900 mg every 7 ± 2 days for 4 weeks, followed by 1200 mg 7 ± 2 days later, then 1200 mg every 14 ± 2 days thereafter. The dosage regimen for pediatric patients weighing less than 40 kg enrolled in Study C09-001r and Study C10-003 was based on body weight [*see Dosage and Administration (2.3)*]. Efficacy evaluations were based on thrombotic microangiopathy (TMA) endpoints.

Endpoints related to TMA included the following:

- platelet count change from baseline
- hematologic normalization *(maintenance of normal platelet counts and LDH levels for at least four weeks)*
- complete TMA response *(hematologic normalization plus at least a 25% reduction in serum creatinine for a minimum of four weeks)*
- TMA-event free status *(absence for at least 12 weeks of a decrease in platelet count of >25% from baseline, plasma exchange or plasma infusion, and new dialysis requirement)*
- Daily TMA intervention rate *(defined as the number of plasma exchange or plasma infusion interventions and the number of new dialyses required per patient per day).*

aHUS Resistant to PE/PI (Study C08-002A/B)

Study C08-002A/B enrolled patients who displayed signs of thrombotic microangiopathy (TMA) despite receiving at least four PE/PI treatments the week prior to screening. One patient had no PE/PI the week prior to screening because of PE/PI intolerance. In order to qualify for enrollment, patients were required to have a platelet count ≤150 x 10^9/L, evidence of hemolysis such as an elevation in serum LDH, and serum creatinine above the upper limits of normal, without the need for chronic dialysis. The median patient age was 28 (range: 17 to 68 years). Patients enrolled in Study C08-002A/B were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 70%-121%. Seventy-six percent of patients had an identified complement regulatory factor mutation or auto-antibody. Table 12 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in Study C08-002A/B.

Table 12: Baseline Characteristics of Patients Enrolled in Study C08-002A/B

Parameter	C08-002A/B (N=17)
Time from aHUS diagnosis until screening in months, median (min, max)	10 (0.26, 236)
Time from current clinical TMA manifestation until screening in months, median (min, max)	<1 (<1, 4)
Baseline platelet count (× 10^9/L), median (range)	118 (62, 161)
Baseline LDH (U/L), median (range)	269 (134, 634)

Patients in Study C08-002A/B received Soliris for a minimum of 26 weeks. In Study C08-002A/B, the median duration of Soliris therapy was approximately 100 weeks (range: 2 weeks to 145 weeks).

Renal function, as measured by eGFR, was improved and maintained during Soliris therapy. The mean eGFR (± SD) increased from 23 ± 15 mL/min/1.73m^2 at baseline to 56 ± 40 mL/min/1.73m^2 by 26 weeks; this effect was maintained through 2 years (56 ± 30 mL/min/1.73m^2). Four of the five patients who required dialysis at baseline were able to discontinue dialysis.

Reduction in terminal complement activity and an increase in platelet count relative to baseline were observed after commencement of Soliris. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. In Study C08-002A/B, mean platelet count (± SD) increased from 109 ± 32 x10^9/L at baseline to 169 ± 72 x10^9/L by one week; this effect was maintained through 26 weeks (210 ± 68 x10^9/L), and 2 years (205 ± 46 x10^9/L). When treatment was continued for more than 26 weeks, two additional patients achieved Hematologic Normalization as well as Complete TMA response. Hematologic Normalization and Complete TMA response were maintained by all responders. In Study C08-002A/B, responses to Soliris were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins.

Table 13 summarizes the efficacy results for Study C08-002A/B.

Table 13: Efficacy Results for Study C08-002A/B

Efficacy Parameter	Study C08-002A/B at 26 wks[1] (N=17)	Study C08-002A/B at 2 yrs[2] (N=17)
Complete TMA response, n (%) Median Duration of complete TMA response, weeks (range)	11 (65) 38 (25, 56)	13 (77) 99 (25, 139)
eGFR improvement ≥15 mL/min/1.73 m^2, n (%) Median duration of eGFR improvement, days (range)	9 (53) 251 (70, 392)	10 (59) ND
Hematologic normalization, n (%) Median Duration of hematologic normalization, weeks (range)	13 (76) 37 (25, 62)	15 (88) 99 (25, 145)
TMA event-free status, n (%)	15 (88)	15 (88)
Daily TMA intervention rate, median (range) Before eculizumab On eculizumab treatment	 0.82 (0.04, 1.52) 0 (0, 0.31)	 0.82 (0.04, 1.52) 0 (0, 0.36)

[1] At data cut-off (September 8, 2010).

[2] At data cut-off (April 20, 2012).

aHUS Sensitive to PE/PI (Study C08-003A/B)

Study C08-003A/B enrolled patients undergoing chronic PE/PI who generally did not display hematologic signs of ongoing thrombotic microangiopathy (TMA). All patients had received PT at least once every two weeks, but no more than three times per week, for a minimum of eight weeks prior to the first Soliris dose. Patients on chronic dialysis were permitted to enroll in Study C08-003A/B. The median patient age was 28 years (range: 13 to 63 years). Patients enrolled in Study C08-003A/B were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 37%-118%. Seventy percent of patients had an identified complement regulatory factor mutation or auto-antibody. Table 14 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in Study C08-003A/B.

Table 14: Baseline Characteristics of Patients Enrolled in Study C08-003A/B

Parameter	Study C08-003A/B (N=20)
Time from aHUS diagnosis until screening in months, median (min, max)	48 (0.66, 286)
Time from current clinical TMA manifestation until screening in months, median (min, max)	9 (1, 45)
Baseline platelet count (× 10^9/L), median (range)	218 (105, 421)
Baseline LDH (U/L), median (range)	200 (151, 391)

Patients in Study C08-003A/B received Soliris for a minimum of 26 weeks. In Study C08-003A/B, the median duration of Soliris therapy was approximately 114 weeks (range: 26 to 129 weeks).

Renal function, as measured by eGFR, was maintained during Soliris therapy. The mean eGFR (± SD) was 31 ± 19 mL/min/1.73m^2 at baseline, and was maintained through 26 weeks (37 ± 21 mL/min/1.73m^2) and 2 years (40 ± 18 mL/min/1.73m^2). No patient required new dialysis with Soliris.

Reduction in terminal complement activity was observed in all patients after the commencement of Soliris. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. Platelet counts were maintained at normal levels despite the elimination of PE/PI. The mean platelet count (± SD) was 228 ± 78 x 10^9/L at baseline, 233 ± 69 x 10^9/L at week 26, and 224 ± 52 x 10^9/L at 2 years. When treatment was continued for more than 26 weeks, six additional patients achieved Complete TMA response. Complete TMA Response and Hematologic Normalization were maintained by all responders. In Study C08-003A/B, responses to Soliris were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins.

Table 15 summarizes the efficacy results for Study C08-003A/B.

Table 15: Efficacy Results for Study C08-003A/B

Efficacy Parameter	Study C08-003A/B at 26 wks[1] (N=20)	Study C08-003A/B at 2 yrs[2] (N=20)
Complete TMA response, n (%) Median duration of complete TMA response, weeks (range)	5 (25) 32 (12, 38)	11 (55) 68 (38, 109)
eGFR improvement ≥15 mL/min/1.73 m^2, n (%)	1 (5)	8 (40)
TMA Event-free status n (%)	16 (80)	19 (95)
Daily TMA intervention rate, median (range) Before eculizumab On eculizumab treatment	 0.23 (0.05, 1.07) 0	 0.23 (0.05, 1.07) 0 (0, 0.01)
Hematologic normalization[4], n (%) Median duration of hematologic normalization, weeks (range)[3]	18 (90) 38 (22, 52)	18 (90) 114 (33, 125)

[1] At data cut-off (September 8, 2010).

[2] At data cut-off (April 20, 2012).

[3] Calculated at each post-dose day of measurement (excluding Days 1 to 4) using a repeated measurement ANOVA model.

[4] In Study C08-003A/B, 85% of patients had normal platelet counts and 80% of patients had normal serum LDH levels at baseline, so hematologic normalization in this population reflects maintenance of normal parameters in the absence of PE/PI.

Retrospective Study in Patients with aHUS (C09-001r)

The efficacy results for the aHUS retrospective study (Study C09-001r) were generally consistent with results of the two prospective studies. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline. Mean platelet count (± SD) increased from 171 ± 83 x10^9/L at baseline to 233 ±109 x10^9/L after one week of therapy; this effect was maintained through 26 weeks (mean platelet count (± SD) at week 26: 254 ± 79 x10^9/L).

A total of 19 pediatric patients (ages 2 months to 17 years) received Soliris in Study C09-001r. The median duration of Soliris therapy was 16 weeks (range 4 to 70 weeks) for children <2 years of age (n=5), 31 weeks (range 19 to 63 weeks) for children 2 to <12 years of age (n=10), and 38 weeks (range 1 to 69 weeks) for patients 12 to <18 years of age (n=4). Fifty-three percent of pediatric patients had an identified complement regulatory factor mutation or auto-antibody.

Overall, the efficacy results for these pediatric patients appeared consistent with what was observed in patients enrolled in Studies C08-002A/B and C08-003A/B (Table 16). No pediatric patient required new dialysis during treatment with Soliris.

Table 16: Efficacy Results in Pediatric Patients Enrolled in Study C09-001r

Efficacy Parameter	<2 yrs (N=5)	2 to <12 yrs (N=10)	12 to <18 yrs (N=4)	Total (N=19)
Complete TMA response, n (%)	2 (40)	5 (50)	1 (25)	8 (42)
Patients with eGFR improvement ≥ 15 mL/min/1.73 m^2, n (%)[2]	2 (40)	6 (60)	1 (25)	9 (47)
Platelet count normalization, n (%)[1]	4 (80)	10 (100)	3 (75)	17 (89)
Hematologic Normalization, n (%)	2 (40)	5 (50)	1 (25)	8 (42)
Daily TMA intervention rate, median (range) Before eculizumab On eculizumab treatment	 1 (0, 2) <1 (0, <1)	 <1 (0.07, 1.46) 0 (0, <1)	 <1 (0, 1) 0 (0, <1)	 0.31 (0.00, 2.38) 0.00 (0.00 , 0.08)

[1] Platelet count normalization was defined as a platelet count of at least 150,000 X 10^9/L on at least two consecutive measurements spanning a period of at least 4 weeks.

[2] Of the 9 patients who experienced an eGFR improvement of at least 15 mL/min/1.73 m^2, one received dialysis throughout the study period and another received Soliris as prophylaxis following renal allograft transplantation.

Adult Patients with aHUS (Study C10-004)

Study C10-004 enrolled patients who displayed signs of thrombotic microangiopathy (TMA). In order to qualify for enrollment, patients were required to have a platelet count < lower limit of normal range (LLN), evidence of hemolysis such as an elevation in serum LDH, and serum creatinine above the upper limits of normal, without the need for chronic dialysis. The median patient age was 35 (range: 18 to 80 years). All patients enrolled in Study C10-004 were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 28%-116%. Fifty-one percent of patients had an identified complement regulatory factor mutation or auto-antibody. A total of 35 patients received PE/PI prior to eculizumab. Table 17 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in Study C10-004.

Table 17: Baseline Characteristics of Patients Enrolled in Study C10-004

Parameter	Study C10-004 (N=41)
Time from aHUS diagnosis until start of study drug in months, median (range)	0.79 (0.03 – 311)
Time from current clinical TMA manifestation until first study dose in months, median (range)	0.52 (0.03-19)
Baseline platelet count ($\times 10^9$/L), median (range)	125 (16 – 332)
Baseline LDH (U/L), median (range)	375 (131 – 3318)

Patients in Study C10-004 received Soliris for a minimum of 26 weeks. In Study C10-004, the median duration of Soliris therapy was approximately 50 weeks (range: 13 weeks to 86 weeks).

Renal function, as measured by eGFR, was improved during Soliris therapy. The mean eGFR (± SD) increased from 17 ± 12 mL/min/1.73m^2 at baseline to 47 ± 24 mL/min/1.73m^2 by 26 weeks. Twenty of the 24 patients who required dialysis at study baseline were able to discontinue dialysis during Soliris treatment.

Reduction in terminal complement activity and an increase in platelet count relative to baseline were observed after commencement of Soliris. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. In Study C10-004, mean platelet count (± SD) increased from 119 ± 66 x10^9/L at baseline to 200 ± 84 x10^9/L by one week; this effect was maintained through 26 weeks (mean platelet count (± SD) at week 26: 252 ± 70 x10^9/L). In Study C10-004, responses to Soliris were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins or auto-antibodies to factor H.

Table 18 summarizes the efficacy results for Study C10-004.

Table 18: Efficacy Results for Study C10-004

Efficacy Parameter	Study C10-004 (N=41)
Complete TMA response, n (%), 95% CI Median duration of complete TMA response, weeks (range)	23 (56) 40,72 42 (6, 75)
Patients with eGFR improvement ≥ 15 mL/min/1.73m^2, n (%)	22 (54)
Hematologic Normalization, n (%) Median duration of hematologic normalization, weeks (range)	36 (88) 46 (10, 75)
TMA Event-free Status, n (%)	37 (90)
Daily TMA Intervention Rate, median (range) Before eculizumab On eculizumab treatment	 0.63 (0, 1.38) 0 (0, 0.58)

Pediatric and Adolescent Patients with aHUS (Study C10-003)

Study C10-003 enrolled patients who were required to have a platelet count < lower limit of normal range (LLN), evidence of hemolysis such as an elevation in serum LDH above the upper limits of normal, serum creatinine level ≥97 percentile for age without the need for chronic dialysis. The median patient age was 6.5 (range: 5 months to 17 years). Patients enrolled in Study C10-003 were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 38%-121%. Fifty percent of patients had an identified complement regulatory factor mutation or auto-antibody. A total of 10 patients received PE/PI prior to eculizumab. Table 19 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in Study C10-003.

Table 19: Baseline Characteristics of Patients Enrolled in Study C10-003

Parameter	Patients 1 month to <12 years (N=18)	All Patients (N=22)
Time from aHUS diagnosis until start of study drug in months, median (range)	0.51 (0.03 – 58)	0.56 (0.03-191)
Time from current clinical TMA manifestation until first study dose in months, median (range)	0.23 (0.03 – 4)	0.2 (0.03-4)
Baseline platelet count (x 10^9/L), median (range)	110 (19-146)	91 (19-146)
Baseline LDH (U/L) median (range)	1510 (282-7164)	1244 (282-7164)

Patients in Study C10-003 received Soliris for a minimum of 26 weeks. In Study C10-003, the median duration of Soliris therapy was approximately 44 weeks (range: 1 dose to 88 weeks).

Renal function, as measured by eGFR, was improved during Soliris therapy. The mean eGFR (± SD) increased from 33 ± 30 mL/min/1.73m^2 at baseline to 98 ± 44 mL/min/1.73m^2 by 26 weeks. Among the 20 patients with a CKD stage ≥2 at baseline, 17 (85%) achieved a CKD improvement of ≥1 stage. Among the 16 patients ages 1 month to <12 years with a CKD stage ≥2 at baseline, 14 (88%) achieved a CKD improvement by ≥1 stage. Nine of the 11 patients who required dialysis at study baseline were able to discontinue dialysis during Soliris treatment. Responses were observed across all ages from 5 months to 17 years of age.

Reduction in terminal complement activity was observed in all patients after commencement of Soliris. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. The mean platelet count (± SD) increased from 88 ± 42 x10^9/L at baseline to 281 ± 123 x10^9/L by one week; this effect was maintained through 26 weeks (mean platelet count (±SD) at week 26: 293 ± 106 x10^9/L). In Study C10-003, responses to Soliris were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins or auto-antibodies to factor H.

Table 20 summarizes the efficacy results for Study C10-003.

Table 20: Efficacy Results for Study C10-003

Efficacy Parameter	Patients 1 month to <12 years (N=18)	All Patients (N=22)
Complete TMA response, n (%) 95% CI Median Duration of complete TMA response, weeks (range)[1]	11 (61) 36, 83 40 (14, 77)	14 (64) 41, 83 37 (14, 77)
eGFR improvement ≥15 mL/min/ 1.73•m^2•n (%)	16 (89)	19 (86)
Complete Hematologic Normalization, n (%) Median Duration of complete hematologic normalization, weeks (range)	14 (78) 38 (14, 77)	18 (82) 38 (14, 77)
TMA Event-Free Status, n (%)	17 (94)	21 (95)
Daily TMA Intervention rate, median (range) Before eculizumab treatment On eculizumab treatment	 0.2 (0, 1.7) 0 (0, 0.01)	 0.4 (0, 1.7) 0 (0, 0.01)

[1.] Through data cutoff (October 12, 2012).

14.3 Generalized Myasthenia Gravis (gMG)

The efficacy of Soliris for the treatment of gMG was established in gMG Study 1 (NCT01997229), a 26-week randomized, double-blind, parallel-group, placebo-controlled, multi-center trial that enrolled patients who met the following criteria at screening:

1. Positive serologic test for anti-AChR antibodies,
2. Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IV,
3. MG-Activities of Daily Living (MG-ADL) total score ≥6,
4. Failed treatment over 1 year or more with 2 or more immunosuppressive therapies (ISTs) either in combination or as monotherapy, or failed at least 1 IST and required chronic plasmapheresis or plasma exchange (PE) or intravenous immunoglobulin (IVIg).

A total of 62 patients were randomized to receive Soliris treatment and 63 were randomized to receive placebo. Baseline characteristics were similar between treatment groups, including age at diagnosis (38 years in each group), gender [66% female (eculizumab) versus 65% female (placebo)], and duration of gMG [9.9 (eculizumab) versus 9.2 (placebo) years]. Over 95% of patients in each group were receiving acetylcholinesterase (AchE) inhibitors, and 98% were receiving immunosuppressant therapies (ISTs). Approximately 50% of each group had been previously treated with at least 3 ISTs.

Soliris was administered according to the recommended dosage regimen [*see Dosage and Administration (2.4)*].

The primary efficacy endpoint for gMG Study 1 was a comparison of the change from baseline between treatment groups in the Myasthenia Gravis-Specific Activities of Daily Living scale (MG-ADL) total score at Week 26. The MG-ADL is a categorical scale that assesses the impact on daily function of 8 signs or symptoms that are typically affected in gMG. Each item is assessed on a 4-point scale where a score of 0 represents normal function and a score of 3 represents loss of ability to perform that function (total score 0-24). A statistically significant difference favoring Soliris was observed in the mean change from baseline to Week 26 in MG-ADL total scores [-4.2 points in the Soliris-treated group compared with -2.3 points in the placebo-treated group (p=0.006)].

A key secondary endpoint in gMG Study 1 was the change from baseline in the Quantitative Myasthenia Gravis (QMG) total score at Week 26. The QMG is a 13-item categorical scale assessing muscle weakness. Each item is assessed on a 4-point scale where a score of 0 represents no weakness and a score of 3 represents severe weakness (total score 0-39). A statistically significant difference favoring Soliris was observed in the mean change from baseline to Week 26 in QMG total scores [-4.6 points in the Soliris-treated group compared with -1.6 points in the placebo-treated group (p=0.001)].

The results of the analysis of the MG-ADL and QMG from gMG Study 1 are shown in Table 21.

Table 21: Analysis of Change from Baseline to Week 26 in MG-ADL and QMG Total Scores in gMG Study 1

Efficacy Endpoints	Soliris-LS Mean (N=62) (SEM)	Placebo-LS Mean (N=63) (SEM)	Soliris change relative to placebo – LS Mean Difference (95% CI)	p-values
MG-ADL	-4.2 (0.49)	-2.3 (0.48)	-1.9 (-3.3, -0.6)	(0.006[a]; 0.014[b])
QMG	-4.6 (0.60)	-1.6 (0.59)	-3.0 (-4.6. -1.3)	(0.001[a]; 0.005[b])

SEM= Standard Error of the Mean;
Soliris-LSMean = least square mean for the treatment group;
Placebo-LSMean = least square mean for the placebo group;
LSMean-Difference (95% CI) = Difference in least square mean with 95% confidence interval;
p-values (testing the null hypothesis that there is no difference between the two treatment arms a: in least square means at Week 26 using a repeated measure analysis; b: in ranks at Week 26 using a worst rank analysis).

In gMG Study 1, a clinical response was defined in the MG-ADL total score as at least a 3-point improvement and in QMG total score as at least a 5-point improvement. The proportion of clinical responders at Week 26 with no rescue therapy was statistically significantly higher for Soliris compared to placebo for both measures. For both endpoints, and also at higher response thresholds (≥4-, 5-, 6-, 7-, or 8-point improvement on MG-ADL, and ≥6-, 7-, 8-, 9-, or 10-point improvement on QMG), the proportion of clinical responders was consistently greater for Soliris compared to placebo. Available data suggest that clinical response is usually achieved by 12 weeks of Soliris treatment.

14.4 Neuromyelitis Optica Spectrum Disorder (NMOSD)

The efficacy of Soliris for the treatment of NMOSD was established in NMOSD Study 1 (NCT01892345), a randomized, double-blind, placebo-controlled trial that enrolled 143 patients with NMOSD who were anti-AQP4 antibody positive and met the following criteria at screening:

1. History of at least 2 relapses in last 12 months or 3 relapses in the last 24 months, with at least 1 relapse in the 12 months prior to screening,
2. Expanded Disability Status Scale (EDSS) score ≤ 7 (consistent with the presence of at least limited ambulation with aid),

3. If on immunosuppressive therapy (IST), on a stable dose regimen,
4. The use of concurrent corticosteroids was limited to 20 mg per day or less,
5. Patients were excluded if they had been treated with rituximab or mitoxantrone within 3 months or with IVIg within 3 weeks prior to screening.

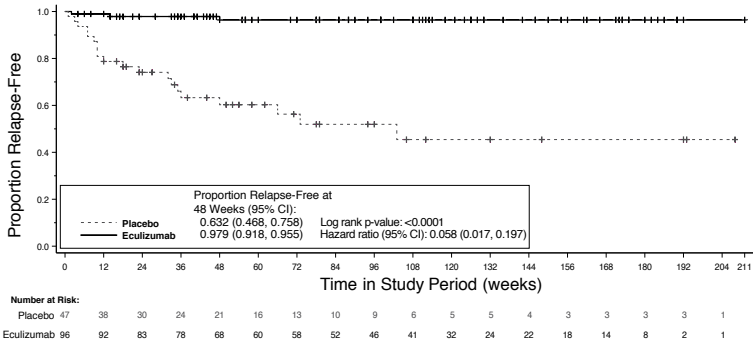
A total of 96 patients were randomized to receive Soliris treatment and 47 were randomized to receive placebo.

The baseline demographic and disease characteristics were balanced between treatment groups. During the treatment phase of the trial, 76% percent of patients received concomitant IST, including chronic corticosteroids; 24% of patients did not receive concomitant IST or chronic corticosteroids during the treatment phase of the trial.

Soliris was administered according to the recommended dosage regimen [*see Dosage and Administration (2.4*)].

The primary endpoint for NMOSD Study 1 was the time to the first adjudicated on-trial relapse. The time to the first adjudicated on-trial relapse was significantly longer in Soliris-treated patients compared to placebo-treated patients (relative risk reduction 94%; hazard ratio 0.058; $p < 0.0001$) (Figure 1).

Figure 1: Kaplan-Meier Survival Estimates for Time to First Adjudicated On-Trial Relapse – Full Analysis Set



Note: Patients who did not experience an adjudicated on-trial relapse were censored at the end of the study period.
Abbreviations: CI = confidence interval

Soliris-treated patients experienced similar improvement in time to first adjudicated on-trial relapse with or without concomitant treatment. Soliris-treated patients had a 96% relative reduction in the adjudicated on-trial annualized relapse rate (ARR) compared to patients on placebo, as shown in Table 22.

Table 22: Adjudicated On-trial Annualized Relapse Rate – Full Analysis Set

Variable	Statistic	Placebo (N = 47)	Soliris (N = 96)
Total number of relapses	Sum	21	3
Adjusted adjudicated ARR[a]	Rate	0.350	0.016
Treatment effect[a]	Rate ratio (eculizumab/placebo)	…	0.045
	p-value	…	<0.0001

[a] Based on a Poisson regression adjusted for randomization strata and historical ARR in 24 months prior to screening.
ARR = annualized relapse rate

Compared to placebo-treated patients, Soliris-treated patients had reduced annualized rates of hospitalizations (0.04 for Soliris versus 0.31 for placebo), of corticosteroid administrations to treat acute relapses (0.07 for Soliris versus 0.42 for placebo), and of plasma exchange treatments (0.02 for Soliris versus 0.19 for placebo).

16 HOW SUPPLIED/STORAGE AND HANDLING

Soliris (eculizumab) injection is a sterile, preservative-free, clear, colorless solution supplied as one 300 mg/30 mL (10 mg/mL) single-dose vial per carton (NDC 25682-001-01).

Store Soliris vials refrigerated at 2º-8º C (36º-46º F) in the original carton to protect from light until time of use. Soliris vials may be stored in the original carton at controlled room temperature (not more than 25° C/77° F) for only a single period up to 3 days. Do not use beyond the expiration date stamped on the carton. Refer to *Dosage and Administration (2)* for information on the stability and storage of diluted solutions of Soliris.

DO NOT FREEZE. DO NOT SHAKE.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read FDA-approved patient labeling (Medication Guide).

Meningococcal Infection

Prior to treatment, patients should fully understand the risks and benefits of Soliris, in particular the risk of meningococcal infection. Ensure that patients receive the Medication Guide.

Inform patients that they are required to receive meningococcal vaccination at least 2 weeks prior to receiving the first dose of Soliris, if they have not previously been vaccinated. They are required to be revaccinated according to current medical guidelines for meningococcal vaccines use while on Soliris therapy. Inform patients that vaccination may not prevent meningococcal infection *[see Warnings and Precautions (5.1)]*.

Signs and Symptoms of Meningococcal Infection

Inform patients about the signs and symptoms of meningococcal infection, 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 a Soliris Patient Safety Information 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 about gonorrhea prevention and advise regular testing for patients at-risk.

Inform patients that there may be an increased risk of other types of infections, particularly those due to encapsulated bacteria.

Aspergillus infections have occurred in immunocompromised and neutropenic patients.

Inform parents or caregivers of children receiving Soliris for the treatment of aHUS that their child should be vaccinated against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) according to current medical guidelines.

Discontinuation

Inform patients with PNH that they may develop hemolysis due to PNH when Soliris is discontinued and that they will be monitored by their healthcare professional for at least 8 weeks following Soliris discontinuation.

Inform patients with aHUS that there is a potential for TMA complications due to aHUS when Soliris is discontinued and that they will be monitored by their healthcare professional for at least 12 weeks following Soliris discontinuation. Inform patients who discontinue Soliris to keep the Soliris Patient Safety Information Card with them for three months after the last Soliris dose, because the increased risk of meningococcal infection persists for several weeks following discontinuation of Soliris.

Manufactured by:

Alexion Pharmaceuticals, Inc.
121 Seaport Boulevard
Boston, MA 02210 USA

US License Number 1743

This product, or its use, may be covered by one or more US patents, including US Patent No. 6,355,245, US Patent No. 9,732,149 and US Patent No. 9,718,880 in addition to others including patents pending.

MEDICATION GUIDE
SOLIRIS® (so-leer-is)
(eculizumab)
injection, for intravenous use

What is the most important information I should know about SOLIRIS?
SOLIRIS is a medicine that affects your immune system. SOLIRIS can lower the ability of your immune system to fight infections.

- **SOLIRIS 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 SOLIRIS if you have not already had this vaccine.
2. If your doctor decided that urgent treatment with SOLIRIS is needed, you should receive meningococcal vaccination as soon as possible.
3. If you have not been vaccinated and SOLIRIS therapy must be initiated immediately, you should also receive two weeks of antibiotics with your vaccinations.
4. If you had a meningococcal vaccine in the past, you might need additional vaccination before starting SOLIRIS. 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

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 3 months after your last SOLIRIS dose. Your risk of meningococcal infection may continue for several weeks after your last dose of SOLIRIS. It is important to show this card to any doctor or nurse who treats you. This will help them diagnose and treat you quickly.
SOLIRIS is only available through a program called the SOLIRIS REMS. Before you can receive SOLIRIS, your doctor must:

- enroll in the SOLIRIS 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 the meningococcal vaccine and, if needed, get revaccinated with the meningococcal vaccine. Ask your doctor if you are not sure if you need to be revaccinated.

SOLIRIS may also increase the risk of other types of serious infections. If your child is treated with SOLIRIS, make sure that your child receives vaccinations against Streptococcus pneumoniae and Haemophilis influenzae type b (Hib). Certain people may be at risk of serious infections with gonorrhea. Talk to your doctor about whether you are at risk for gonorrhea infection, about gonorrhea prevention, and regular testing. Certain fungal infections (aspergillus) may also happen if you take SOLIRIS and have a weak immune system or a low white blood cell count.

What is SOLIRIS?

SOLIRIS is a prescription medicine called a monoclonal antibody. SOLIRIS is used to treat:

- patients- with a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH).
- adults and children with a disease called atypical Hemolytic Uremic Syndrome (aHUS). SOLIRIS is not for use in treating people with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).
- adults with a disease called generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AchR) antibody positive
- adults with a disease called neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody positive.

It is not known if SOLIRIS is safe and effective in children with PNH, gMG, or NMOSD.

Who should not receive SOLIRIS?

Do not receive SOLIRIS if you:

- have a meningococcal infection.
- have not been vaccinated against meningitis infection unless your doctor decides that urgent treatment with SOLIRIS is needed. See "What is the most important information I should know about SOLIRIS?"

Before you receive SOLIRIS, 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 SOLIRIS will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if SOLIRIS passes into your breast milk.

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

It is important that you:

- have all recommended vaccinations before you start SOLIRIS.
- receive 2 weeks of antibiotics if you immediately start SOLIRIS.
- stay up-to-date with all recommended vaccinations during treatment with SOLIRIS.

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 SOLIRIS?

- SOLIRIS is given through a vein (I.V. or intravenous infusion) usually over 35 minutes in adults and 1 to 4 hours in pediatric patients. If you have an allergic reaction during your SOLIRIS infusion, your doctor may decide to give SOLIRIS more slowly or stop your infusion.
- If you are an adult, you will usually receive a SOLIRIS infusion by your doctor:
  - weekly for five weeks, then
  - every 2 weeks
- **If you** are less than 18 years of age, your doctor will decide how often you will receive SOLIRIS depending on your age and body weight
- After each infusion, you should be monitored for one hour for allergic reactions. See "What are the possible side effects of SOLIRIS?"
- If you miss a SOLIRIS infusion, call your doctor right away.
- **If you have PNH, your doctor will need to monitor you closely for at least 8 weeks after stopping SOLIRIS. Stopping treatment with SOLIRIS 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
  - drop in your platelet counts
  - confusion
  - difficulty breathing
  - kidney problems
  - blood clots
  - chest pain
- **If you have aHUS, your doctor will need to monitor you closely during and for at least 12 weeks after stopping treatment for signs of worsening aHUS symptoms or problems related to abnormal clotting (thrombotic microangiopathy).**

  Symptoms or problems that can happen with abnormal clotting may include:
  - stroke
  - confusion
  - seizure
  - chest pain (angina)
  - difficulty breathing
  - kidney problems
  - swelling in arms or legs
  - a drop in your platelet count

What are the possible side effects of SOLIRIS?

SOLIRIS can cause serious side effects including:

- See **"What is the most important information I should know about SOLIRIS?"**
- **Serious allergic reactions.** Serious allergic reactions can happen during your SOLIRIS infusion. Tell your doctor or nurse right away if you get any of these symptoms during your SOLIRIS infusion:
  - chest pain
  - trouble breathing or shortness of breath
  - swelling of your face, tongue, or throat
  - feel faint or pass out

If you have an allergic reaction to SOLIRIS, your doctor may need to infuse SOLIRIS more slowly, or stop SOLIRIS. See "How will I receive SOLIRIS?"

The most common side effects in people with PNH treated with SOLIRIS include:

- headache
- pain or swelling of your nose or throat (nasopharyngitis)
- back pain
- nausea

The most common side effects in people with aHUS treated with SOLIRIS include:

- headache
- diarrhea
- high blood pressure (hypertension)
- common cold (upper respiratory infection)
- stomach-area (abdominal pain)
- vomiting
- pain or swelling of your nose or throat (nasopharyngitis)
- low red blood cell count (anemia)
- cough
- swelling of legs or feet (peripheral edema
- nausea
- urinary tract infections
- fever

The most common side effects in people with gMG treated with SOLIRIS include:

- muscle and joint (musculoskeletal) pain

The most common side effects in people with NMOSD treated with SOLIRIS include:

- common cold (upper respiratory infection)
- pain or swelling of your nose or throat (nasopharyngitis)
- diarrhea
- back pain
- dizziness
- flu like symptoms (influenza) including fever, headache, tiredness, cough, sore throat, and body aches
- joint pain (arthralgia)
- throat irritation (pharyngitis)
- bruising (contusion)

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 SOLIRIS. 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 SOLIRIS.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SOLIRIS for a condition for which it was not prescribed. Do not give SOLIRIS to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or doctor for information about SOLIRIS that is written for health professionals.

What are the ingredients in SOLIRIS?

Active ingredient: eculizumab

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. US License Number 1743

This Medication Guide has been approved by the U.S. Food and Drug Administration
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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ULTOMIRIS™ safely and effectively. See full prescribing information for ULTOMIRIS.

ULTOMIRIS™ (ravulizumab-cwvz) injection, for intravenous use

Initial U.S. Approval: 2018

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

See full prescribing information for complete boxed warning

Life-threatening meningococcal infections/sepsis have occurred in patients treated with ULTOMIRIS and may become rapidly life-threatening or fatal if not recognized and treated early (5.1).

- **Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies (5.1).**
- **Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of ULTOMIRIS, unless the risks of delaying ULTOMIRIS therapy outweigh the risks 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.**
- **Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.**

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 (5.1).

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Only administer as an intravenous infusion.

Weight-Based Dosage Regimen: (2.1)

Body Weight Range (kg)	Loading Dose (mg)	Maintenance Dose (mg)
greater or equal to 40 to less than 60	2,400	3,000
greater than or equal to 60 to less than 100	2,700	3,300
greater than or equal to 100	3,000	3,600

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

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

Life-threatening meningococcal infections/sepsis have occurred in patients treated with ULTOMIRIS. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early *[see Warnings and Precautions (5.1)]*.

- **Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.**
- **Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of ULTOMIRIS, unless the risks of delaying ULTOMIRIS therapy outweigh 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 infections. Monitor patients for early signs of meningococcal infections and evaluate immediately if infection is suspected.**

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 *[see Warnings and Precautions (5.1)]*. Enrollment in the ULTOMIRIS REMS program and additional information are available by telephone: 1-844-259-6783 or at www.ultomirisrems.com.

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Vaccination and Prophylaxis

Vaccinate patients for meningococcal disease according to current ACIP guidelines to reduce the risk of serious infection *[see Warnings and Precautions (5.1, 5.2)]*.

Provide 2 weeks of antibacterial drug prophylaxis to patients if ULTOMIRIS must be initiated immediately and vaccines are administered less than 2 weeks before starting ULTOMIRIS therapy.

Healthcare professionals who prescribe ULTOMIRIS must enroll in the ULTOMIRIS REMS *[see Warnings and Precautions (5.1)]*.

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.

Table 1: ULTOMIRIS Weight-Based Dosing Regimen

Body Weight Range (kg)	Loading Dose (mg)	Maintenance Dose (mg)
greater than or equal to 40 to less than 60	2,400	3,000
greater than or equal to 60 to less than 100	2,700	3,300
greater than or equal to 100	3,000	3,600

2.3 Preparation and Administration

Preparation of ULTOMIRIS

Each vial of ULTOMIRIS is intended for single-dose only.

ULTOMIRIS requires dilution to a final concentration of 5 mg/mL.

Use aseptic technique to prepare ULTOMIRIS as follows:

1. The number of vials to be diluted is determined based on the individual patient's weight and the prescribed dose *[see Dosage and Administration (2.2)]*.
2. Prior to dilution, visually inspect the solution in the vials; the solution should be free of any particulate matter or precipitation. Do not use if there is evidence of particulate matter or precipitation.
3. Withdraw the calculated volume of ULTOMIRIS from the appropriate number of vials and dilute in an infusion bag using 0.9% Sodium Chloride Injection, USP to a final concentration of 5 mg/mL. Refer to the administration reference tables below. The product should be mixed gently. Do not shake. Protect from light. Do not freeze.
4. Administer the prepared solution immediately following preparation. Refer to the administration reference tables below for minimum infusion duration. Infusion must be administered through a 0.22 micron filter.
5. If the diluted ULTOMIRIS infusion solution is not used immediately, storage under refrigeration at 2°C – 8°C (36°F – 46°F) must not exceed 24 hours taking into account the expected infusion time. Once removed from refrigeration, administer the diluted ULTOMIRIS infusion solution within 6 hours.

Administration of ULTOMIRIS

Only administer as an intravenous infusion.

Dilute ULTOMIRIS to a final concentration of 5 mg/mL.

Administer ULTOMIRIS only through a 0.22 micron filter.

Table 2: Loading Dose Administration Reference Table

Body Weight Range (kg)[a]	Loading Dose (mg)	ULTOMIRIS Volume (mL)	Volume of NaCl Diluent[b] (mL)	Total Volume (mL)	Maximum Infusion Rate (mL/hr)
greater than or equal to 40 to less than 60	2,400	240	240	480	252
greater than or equal to 60 to less than 100	2,700	270	270	540	317
greater than or equal to 100	3,000	300	300	600	333

[a] Body weight at time of treatment

[b] Dilute ULTOMIRIS only using 0.9% Sodium Chloride Injection, USP.

Table 3: Maintenance Dose Administration Reference Table

Body Weight Range (kg)[a]	Maintenance Dose (mg)	ULTOMIRIS Volume (mL)	Volume of NaCl Diluent[b] (mL)	Total Volume (mL)	Maximum Infusion Rate (mL/hr)
greater than or equal to 40 to less than 60	3,000	300	300	600	257
greater than or equal to 60 to less than 100	3,300	330	330	660	330
greater than or equal to 100	3,600	360	360	720	327

[a] Body weight at time of treatment

[b] 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 Prevention

Life-threatening meningococcal infections have occurred in patients treated with ULTOMIRIS. The use of ULTOMIRIS increases a patient's susceptibility to serious meningococcal infections (septicemia 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 steps 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.

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, shortness of breath (dyspnea), 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 alter anticoagulant management.

5.5 Infusion Reactions

Administration of ULTOMIRIS may 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. 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 adverse 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 Naïve and Eculizumab-Experienced Patients with PNH

	Number of Patients	
Body System Adverse Reaction	ULTOMIRIS (n=222) n (%)	Eculizumab (n=219) n (%)
Gastrointestinal disorders		
Diarrhea	19 (9)	12 (5)
Nausea	19 (9)	19 (9)
Abdominal pain	13 (6)	16 (7)
General Disorders and Administration Site Conditions		
Pyrexia	15 (7)	18 (8)
Infections and Infestations		
Upper respiratory tract infection[a]	86 (39)	86 (39)
Musculoskeletal and Connective Tissue Disorders		
Pain in extremity	14 (6)	11 (5)
Arthralgia	11 (5)	12 (5)
Nervous System Disorders		
Headache	71 (32)	57 (26)
Dizziness	12 (5)	14 (6)

[a] Grouped term includes: Nasopharyngitis, Upper respiratory tract infection, Oropharyngeal pain, Viral upper respiratory tract infection, Rhinitis, Respiratory tract infection, Rhinorrhoea, Pharyngitis, and Upper respiratory tract inflammation

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity 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 ravulizumab products 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 206 (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 paroxysmal nocturnal 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 moribund offspring at doses 0.8-2.2 times the human dose *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or fetal/neonatal risk

PNH in pregnancy is associated with adverse maternal outcomes, including worsening cytopenias, thrombotic events, infections, bleeding, miscarriages, and increased maternal mortality, and adverse fetal outcomes, including fetal death and premature delivery.

Data

Animal Data

Animal reproduction studies were conducted in mice using doses of a murine anti-C5 antibody that approximated 1-2.2 times (loading dose) and 0.8-1.8 times (maintenance dose) the recommended human ULTOMIRIS dose, based on a body weight comparison. When animal exposure to the antibody occurred in the time period from before mating until early gestation, no decrease in fertility or reproductive performance was observed. When maternal exposure to the antibody occurred during organogenesis, two cases of retinal dysplasia and one case of umbilical hernia were observed among 230 offspring born to mothers exposed to the higher antibody dose; however, the exposure did not increase fetal loss or neonatal death. When maternal exposure to the antibody occurred in the time period from implantation through weaning, a higher number of male offspring became moribund or died (1/25 controls, 2/25 low dose group, 5/25 high dose group). Surviving offspring had normal development and reproductive function. Human IgG are known to cross the human placental barrier, and thus ULTOMIRIS may potentially cause terminal complement inhibition in the fetal circulation.

8.2 Lactation

Risk summary

There are no data on the presence of ravulizumab-cwvz in human milk, the effect on the breastfed child, or the effect on milk production. Since many medicinal products and immunoglobulins are secreted into human milk, and because of the potential for serious adverse reactions in a nursing child, breastfeeding should be discontinued during treatment and for 8 months after the final dose.

8.4 Pediatric Use

The safety and efficacy of ULTOMIRIS in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of ULTOMIRIS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

11 DESCRIPTION

Ravulizumab-cwvz, a complement inhibitor, is a humanized monoclonal antibody (mAb) produced in Chinese hamster ovary (CHO) cells. Ravulizumab-cwvz consists of 2 identical 448 amino acid heavy chains and 2 identical 214 amino acid light chains and has a molecular weight of approximately 148 kDa. The constant regions of ravulizumab-cwvz include the human kappa light chain constant region, and the protein engineered "IgG2/4" heavy chain constant region.

The heavy chain CH1 domain, hinge region, and the first 5 amino acids of the CH2 domain match the human IgG2 amino acid sequence, residues 6 to 36 in the CH2 region (common to both human IgG2 and IgG4 amino acid sequences), while the remainder of the CH2 domain and the CH3 domain match the human IgG4 amino acid sequence. The heavy and light chain variable regions that form the human C5 binding site consist of human framework regions grafted to murine complementarity-determining regions.

ULTOMIRIS (ravulizumab-cwvz) injection is a sterile, clear to translucent, slight whitish color, preservative-free solution for intravenous use. Each single-dose vial contains 300 mg ravulizumab-cwvz at a concentration of 10 mg/mL with a pH of 7.0. Each mL also contains polysorbate 80 (0.2 mg) (vegetable origin), sodium chloride (8.77 mg), sodium phosphate dibasic (1.78 mg), sodium phosphate monobasic (0.46 mg), and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ravulizumab-cwvz is a terminal complement inhibitor that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the terminal complement complex [C5b-9]) and preventing the generation of the terminal complement complex C5b9. ULTOMIRIS inhibits terminal complement-mediated intravascular hemolysis in patients with PNH.

12.2 Pharmacodynamics

Immediate and complete inhibition of serum free C5 (concentration of less than 0.5 mcg/mL) was observed by the end of the first ULTOMIRIS infusion and sustained throughout the entire 26-week treatment period in all patients, both complement-inhibitor naïve and previously treated with eculizumab.

The extent and duration of the pharmacodynamic response in patients with PNH were exposure dependent for ULTOMIRIS. Free C5 levels of <0.5 mcg/mL were correlated with maximal intravascular hemolysis control and complete terminal complement inhibition.

Complete terminal complement inhibition following initiation of ULTOMIRIS treatment led to normalization of serum LDH by week 4 in complement-inhibitor naïve patients, and maintained LDH normalization in patients previously treated with eculizumab *[see Clinical Studies (14)]*.

12.3 Pharmacokinetics

Ravulizumab-cwvz pharmacokinetics increase proportionally over a dose range of 200 to 5400 mg. Ravulizumab-cwvz C_{max} and C_{trough} parameters are presented in Table 5.

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

		N	Complement Inhibitor-Naïve	N	Previously Treated with Eculizumab
C_{max} (mcg/mL)	LD	125	771 ± 166 (21.5)	95	843 ± 204 (24.1)
	MD	124	1379 ± 276 (20.0)	95	1386 ± 268 (19.4)
C_{trough} (mcg/mL)	LD	125	391 ± 137 (35.0)	96	405 ± 121 (29.9)
	MD	124	473 ± 158 (33.4)	95	501 ± 143 (28.6)

LD = Loading Dose; MD = Maintenance Dose

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-cwvz 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-cwvz 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-cwvz pharmacokinetics is unknown.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal carcinogenicity studies of ravulizumab-cwvz have not been conducted.

Genotoxicity studies have not been conducted with ravulizumab-cwvz.

Effects of ravulizumab-cwvz upon fertility have not been studied in animals. Intravenous 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 until 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 cells 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 88%, 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

Parameter	Statistics	ULTOMIRIS (N = 125)	Eculizumab (N = 121)
Age (years) at first infusion in study	Mean (SD) Min, max	44.8 (15.2) 18, 83	46.2 (16.2) 18, 86
Sex Male	n (%)	65 (52.0)	69 (57.0)
Race Asian White Black or African American American Indian or Alaska Native Other Not reported	n (%)	 72 (57.6) 43 (34.4) 2 (1.6) 1 (0.8) 4 (3.2) 3 (2.4)	 57 (47.1) 51 (42.1) 4 (3.3) 1 (0.8) 4 (3.3) 4 (3.3)
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, 44)	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 MAVE[b]	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)

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

[b] 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

	ULTOMIRIS (N=125)	Eculizumab (N=121)	Statistic for Comparison	Treatment Effect (95% CI)
Transfusion avoidance rate	73.6%	66.1%	Difference in rate	6.8 (-4.66, 18.14)
LDH normalization	53.6%	49.4%	Odds ratio	1.19 (0.80, 1.77)
LDH percent change	-76.84%	-76.02%	Difference in % change from baseline	-0.83 (-5.21, 3.56)
Breakthrough hemolysis	4.0%	10.7%	Difference in rate	-6.7 (-14.21, 0.18)
Hemoglobin stabilization	68.0%	64.5%	Difference in rate	2.9 (-8.80, 14.64)

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 FACIT-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

Parameter	Statistics	ULTOMIRIS (N = 97)	Eculizumab (N = 98)
Age (years) at first infusion in study	Mean (SD) Min, max	46.6 (14.41) 18, 79	48.8 (13.97) 23, 77
Race White Asian Black or African American Other Not reported Unknown Multiple	n (%)	 50 (51.5) 23 (23.7) 5 (5.2) 2 (2.1) 13 (13.4) 3 (3.1) 1 (1.0)	 61 (62.2) 19 (19.4) 3 (3.1) 1 (1.0) 13 (13.3) 1 (1.0) 0
Sex Male	n (%)	 50 (51.5)	 48 (49.0)
Pre-treatment LDH levels (U/L)	Median Min, max	224.0 135.0, 383.5	234.0 100.0, 365.5
Units of pRBC/whole blood transfused within 12 months prior to first dose	Median Min, max	4.0 (1, 32)	2.5 (2, 15)
Antithrombotic agents used within 28 days prior to first dose	n (%)	20 (20.6)	13 (13.3)
Patients with a history of MAVE[a]	n (%)	28 (28.9)	22 (22.4)
Patients with a history of thrombosis	n (%)	27 (27.8)	21 (21.4)
Patients with concomitant anticoagulant treatment	n (%)	22 (22.7)	16 (16.3)

[a] 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

	ULTOMIRIS n = 97	Eculizumab n = 98	Statistic for Comparison	Treatment Effect (95% CI)
LDH Percent change	-0.82%	8.4%	Difference in % change from baseline	9.2 (-0.42, 18.8)
Breakthrough hemolysis	0%	5.1%	Difference in rate	5.1 (-8.9, 19.0)
Transfusion avoidance	87.6%	82.7%	Difference in rate	5.5 (-4.3, 15.7)
Hemoglobin Stabilization	76.3%	75.5%	Difference in rate	1.4 (-10.4, 13.3)

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 FACIT-fatigue instrument. Patient-reported fatigue may be an under- or over-estimation, because patients were not blinded to treatment assignment.

16 HOW SUPPLIED/STORAGE AND HANDLING

ULTOMIRIS (ravulizumab-cwvz) injection is a clear to translucent, slight whitish color preservative-free, solution supplied as one 300 mg/30 mL (10 mg/mL) single-dose vial per carton. NDC 25682-022-01.

Store ULTOMIRIS vials refrigerated at 2°C – 8°C (36°F – 46°F) in the original carton to protect from light. Do not freeze. Do not shake.

Refer to Dosage and Administration (2.3) for information on the stability and storage of diluted solutions of ULTOMIRIS.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read FDA-approved patient labeling (Medication Guide).

Meningococcal Infection

Advise patients of the risk of meningococcal infection/sepsis. Inform patients that they are required to receive meningococcal vaccination at least 2 weeks prior to receiving the first dose of ULTOMIRIS, if they have not previously been vaccinated. They are required to be revaccinated 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.

Manufactured by:

Alexion Pharmaceuticals, Inc.
121 Seaport Boulevard
Boston, MA 02210 USA

US License Number 1743

This product, or its use, may be covered by one or more US patents, including US Patent No. 9,371,377; 9,079,949 and 9,663,574 in addition to others including patents pending.

ULTOMIRIS is a trademark of Alexion Pharmaceuticals, Inc.

MEDICATION GUIDE

ULTOMIRIS™ (ul-toe-meer′-is)
(ravulizumab-cwvz)
injection, for intravenous use

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

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 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
  - ○ 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

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