Soliris® (eculizumab) 
Initiation Guide

Soliris is FDA-approved to treat adult patients with:

• Anti-acetylcholine receptor (AChR) antibody-positive generalized myasthenia gravis (gMG)
• Anti-aquaporin-4 (AQP4) antibody-positive neuromyelitis optica spectrum disorder (NMOSD)

SELECT IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

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.

• 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 Serious Meningococcal Infections 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. 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.

Please see Important Safety Information throughout and accompanying full Prescribing Information for Soliris, including Boxed WARNING regarding serious meningococcal infections.
Enroll in REMS

Due to the risk of meningococcal infections, prescribers must enroll in our Risk Evaluation and Mitigation Strategy (REMS) program to obtain Soliris® (eculizumab). Call Customer Operations at 1-888-SOLIRIS (1-888-765-4747) or visit SolirisREMS.com to learn more and enroll.

You must be specifically certified to prescribe Soliris. Certification consists of review of REMS educational materials and enrollment in the Soliris REMS.

Review the Soliris REMS HCP educational materials

- Prescribing Information
- Prescriber Safety Brochure
- Patient Safety Brochure
- Soliris Patient Safety Card

Enroll in the Soliris REMS program

Complete the Soliris REMS Prescriber Enrollment online OR print and sign the Prescriber Enrollment Form.

- Mail the form to Soliris REMS, Alexion Pharmaceuticals, 121 Seaport Boulevard, Boston, MA 02210
- Fax the form to Soliris REMS at 1-877-580-ALXN (1-877-580-2596)
- Scan and email the form to rems@alexion.com

Visit SolirisREMS.com for more information.

SELECT IMPORTANT SAFETY INFORMATION

Contraindications

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

Please see Important Safety Information throughout and accompanying full Prescribing Information for Soliris, including Boxed WARNING regarding serious meningococcal infections.
Meningococcal vaccinations

Immunize patients with both types of meningococcal vaccines at least 2 weeks before starting treatment with Soliris® (eculizumab)

The 2020 Advisory Committee on Immunization Practices (ACIP) recommends the following meningococcal vaccination regimens for patients with persistent complement component deficiency or in patients receiving complement inhibitors, including patients receiving Soliris.

Vaccinations are necessary before treatment with Soliris

- The use of Soliris increases a patient’s susceptibility to life-threatening and fatal meningococcal infections (septicemia and/or meningitis), which have occurred in patients treated with Soliris.
- Comply with the most current ACIP recommendations for meningococcal vaccination in patients with complement deficiencies and patients receiving a complement inhibitor.
- Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of Soliris, unless the risks of delaying therapy outweigh the risk of developing a meningococcal infection.
- If urgent Soliris therapy is indicated in an unvaccinated patient, initiate the vaccine regimen as soon as possible and provide 2 weeks of antibacterial drug prophylaxis.

Please refer to the most up-to-date ACIP recommendations for the most current and complete information for meningococcal vaccination in persons with persistent complement component deficiencies and patients treated with complement inhibitors, such as Soliris.
Monitoring patients

Monitoring patients receiving Soliris® (eculizumab) for early signs and symptoms of meningococcal infections

Vaccination reduces, but does not eliminate, the risk of meningococcal infections. Advise patients to seek immediate medical attention if these signs or symptoms occur. Meningococcal infections may become rapidly life-threatening if not recognized and treated early.

Signs and symptoms of meningococcal infections include:

- Headache with nausea or vomiting
- Headache and fever
- Headache with a stiff neck or back
- Fever with or without a rash
- Confusion
- Muscle aches with flu-like symptoms
- Eyes sensitive to light

Evaluate patients immediately if an infection is suspected.

Discontinue Soliris in patients who are undergoing treatment for serious meningococcal infections.

See additional information on monitoring patients for infusion reactions on page 9.

SELECT IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Serious Meningococcal Infections

Risk and Prevention

The use of Soliris increases a patient’s susceptibility to serious meningococcal infections (septicemia and/or meningitis).

Please see Important Safety Information throughout and accompanying full Prescribing Information for Soliris, including Boxed WARNING regarding serious meningococcal infections.
Soliris® (eculizumab) recommended dosage regimen

For adult patients with anti-AChR antibody-positive gMG or anti-AQP4 antibody-positive NMOSD (≥18 years of age), Soliris treatment begins with an induction phase and is followed by a maintenance phase.

<table>
<thead>
<tr>
<th>INDUCTION PHASE</th>
<th>MAINTENANCE PHASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>900 mg given as IV infusion once weekly for 4 weeks</td>
<td>1200 mg given as IV infusion once at week 5</td>
</tr>
<tr>
<td>1200 mg given as IV infusion every 2 weeks thereafter</td>
<td></td>
</tr>
</tbody>
</table>

Administer Soliris at the recommended dosage regimen time points, or within 2 days of these time points. Ensure patients understand that they should adhere to the recommended dosing regimen consistently unless otherwise advised by you.

Supplemental dosing

Supplemental dosing of Soliris is required in patients receiving concomitant plasmapheresis, plasma exchange, or fresh frozen plasma infusion.

<table>
<thead>
<tr>
<th>Type of plasma intervention</th>
<th>Most recent Soliris dose</th>
<th>Supplemental Soliris dose with each plasma intervention</th>
<th>Timing of supplemental Soliris dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasmapheresis or plasma exchange</td>
<td>300 mg</td>
<td>300 mg per each plasmapheresis or plasma exchange session</td>
<td>Within 60 minutes after each plasmapheresis or plasma exchange session</td>
</tr>
<tr>
<td>≥600 mg</td>
<td>600 mg per each plasmapheresis or plasma exchange session</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>≥300 mg</td>
<td>300 mg per infusion of fresh frozen plasma</td>
<td>60 minutes prior to each infusion of fresh frozen plasma</td>
</tr>
</tbody>
</table>

SELECT IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Serious Meningococcal Infections
Risk and Prevention (continued)

Vaccinate or revaccinate for meningococcal disease according to the most current ACIP recommendations for patients with complement deficiencies. Immunize patients without a history of meningococcal vaccination at least 2 weeks prior to receiving the first dose of Soliris. If Soliris must be initiated immediately in an unvaccinated patient, administer meningococcal vaccine(s) as soon as possible and provide 2 weeks of antibacterial drug prophylaxis. Discontinue Soliris in patients who are undergoing treatment for serious meningococcal infections.

Please see Important Safety Information throughout and accompanying full Prescribing Information for Soliris, including Boxed WARNING regarding serious meningococcal infections.
How to write a prescription for Soliris® (eculizumab)

Treatment begins with 900 mg infusions once a week for 4 weeks, followed by 1200 mg infusions once at week 5 and every 2 weeks thereafter.¹

Administer Soliris at the recommended dosage regimen time points or within 2 days of these time points.¹

**Treatment sites**

Soliris is a treatment that is given by intravenous (IV) infusion.¹ Depending on the patient’s insurance and location, infusions can be administered at:

- A doctor’s office
- An infusion center
- A patient’s home

A OneSource Case Manager can assist your patients with locating an infusion center.

---

**SELECT IMPORTANT SAFETY INFORMATION**

**Warnings and Precautions**

**Serious Meningococcal Infections**

**REMS**

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).

Please see Important Safety Information throughout and accompanying full Prescribing Information for Soliris, including Boxed WARNING regarding serious meningococcal infections.
Ordering and storing Soliris® (eculizumab)

Place your order with an authorized specialty distributor, OR send your completed prescription to the payer-designated specialty pharmacy.

An Alexion Customer Operations Representative will work with either party to facilitate order processing and delivery.

Storage and handling

- Store Soliris vials in the original carton to protect from light until time of use, refrigerated at 2°C to 8°C (36°F to 46°F).
- Soliris vials may be stored in the original carton at a 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 the Prescribing Information (section 2 Dosage and Administration) for information on the stability and storage of diluted solutions of Soliris.
- DO NOT FREEZE; DO NOT SHAKE.

Ordering Soliris:
NDC 25682-001-01 SINGLE-UNIT, 300 mg/30 mL (10 mg/mL)
SINGLE-DOSE VIAL PER CARTON

SELECT IMPORTANT SAFETY INFORMATION

Warnings and Precautions
Other Infections
Serious infections with Neisseria species (other than N. meningitidis), including disseminated gonococcal infections, have been reported.

Patients may have increased susceptibility to infections, especially with encapsulated bacteria. Additionally, Aspergillus infections have occurred in immunocompromised and neutropenic patients. Use caution when administering Soliris to patients with any systemic infection.

Please see Important Safety Information throughout and accompanying full Prescribing Information for Soliris, including Boxed WARNING regarding serious meningococcal infections.
Preparing and administering Soliris® (eculizumab)

It is important to carefully adhere to the following preparation and administration instructions for Soliris.

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 meningococcal infections.

1. **Inspect the vial**
   Soliris is supplied in 300 mg, single-dose vials containing 30 mL (10 mg/mL) of sterile, preservative-free solution. Prior to administration, inspect Soliris vials for particulate matter and discoloration. Soliris should be clear and colorless.

2. **Dilute the solution**
   Prior to administration, dilute Soliris to a final concentration of 5 mg/mL. Choose one of the following diluents:
   - 0.9% sodium chloride injection, USP
   - 0.45% sodium chloride injection, USP
   - 5% dextrose in water injection, USP
   - Ringer’s injection, USP

   **a.** Withdraw the required amount of Soliris from the vial into a sterile syringe and transfer the recommended dose to an infusion bag.

   **b.** Dilute Soliris to a final concentration of 5 mg/mL by adding the appropriate amount of diluent, using the table below as a guideline. The volume of diluent should be equal to the drug volume.

<table>
<thead>
<tr>
<th>Soliris dose</th>
<th>Diluent volume</th>
<th>Final volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg</td>
<td>30 mL</td>
<td>60 mL</td>
</tr>
<tr>
<td>600 mg</td>
<td>60 mL</td>
<td>120 mL</td>
</tr>
<tr>
<td>900 mg</td>
<td>90 mL</td>
<td>180 mL</td>
</tr>
<tr>
<td>1200 mg</td>
<td>120 mL</td>
<td>240 mL</td>
</tr>
</tbody>
</table>

SELECT IMPORTANT SAFETY INFORMATION

**Infusion Reactions**
Administration of Soliris may result in infusion reactions, including anaphylaxis or other hypersensitivity reactions. Interrupt Soliris infusion and institute appropriate supportive measures if signs of cardiovascular instability or respiratory compromise occur.

Please see Important Safety Information throughout and accompanying full Prescribing Information for Soliris, including Boxed WARNING regarding serious meningococcal infections.
Invert the infusion bag

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

- Allow the admixture to adjust to room temperature prior to administration (18°C to 25°C or 64°F to 77°F); it must not be heated in a microwave or with any heat source other than ambient air temperature.

- Inspect visually for particulate matter and discoloration prior to administration.

- The admixed solution of Soliris is stable for 24 hours at 2°C to 8°C (36°F to 46°F) and at room temperature.

Administer the IV infusion

- Soliris should only be administered by IV infusion. Administer over 35 minutes via gravity feed, a syringe-type pump, or an infusion pump. Do not administer as an IV push or bolus injection.

Monitoring for adverse reactions during and after Soliris administration

If an adverse reaction occurs during 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 2 hours.

- Monitor the patient during the infusion and for at least 1 hour following completion for signs or symptoms of an infusion reaction. These can include anaphylaxis or other hypersensitivity reactions.

- Interrupt Soliris infusion and institute appropriate supportive measures if signs of cardiovascular instability or respiratory compromise occur.

SELECT IMPORTANT SAFETY INFORMATION

Adverse Reactions

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

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.

Please see Important Safety Information throughout and accompanying full Prescribing Information for Soliris, including Boxed WARNING regarding serious meningococcal infections.
Begin with OneSource™

Connect patients to OneSource for ongoing support

OneSource is a complimentary, personalized patient support program offered by Alexion available for eligible enrolled adult patients with anti-AChR antibody-positive gMG and adult patients with anti-AQP4 antibody-positive NMOSD. OneSource Case Managers have advanced training in rare conditions, health insurance expertise, and information about community resources. OneSource offers assistance with:

- **Health insurance navigation**
  - Helping patients understand their health insurance coverage for Soliris® (eculizumab)
  - Providing information on external funding resources for out-of-pocket costs and exploring alternative options for gaps in coverage and funding issues or concerns
  - Supporting patients in locating infusion sites or home infusion options based on patient preference, plan of care, and health plan requirements

- **Education**
  - Providing patients with educational and supporting materials, such as brochures and website resources
  - Safety education regarding Soliris

- **Ongoing support**
  - Providing personalized support during major life events, such as a change in insurance status, travel, or relocation
  - Exploring alternative infusion locations while patients travel, based on patient/provider preference and health plan requirements

- **Community connections**
  - Providing information about in-person and online meetings and events
  - Connecting patients with rare disease communities and advocacy groups

Contact OneSource at **1-888-765-4747** or via email at **OneSource@Alexion.com**.

Please see Important Safety Information throughout and accompanying full Prescribing Information for Soliris, including Boxed WARNING regarding serious meningococcal infections.
The Alexion OneSource CoPay Program helps patients pay for eligible out-of-pocket medication and infusion costs. For more information, please visit [www.AlexionOneSource.com/CoPay](http://www.AlexionOneSource.com/CoPay).

**Who is eligible for this Program?**

- Patient enrolled in OneSource
- Patient with commercial insurance who has a valid prescription for a US Food and Drug Administration–approved indication for Soliris® (eculizumab)
- Patient must be a citizen or permanent resident of the United States or its territories

**How can my patient apply for the Program?**

**Fill out the Alexion OneSource CoPay Program Enrollment Form**

The enrollment form can be found at [www.AlexionOneSource.com/CoPayForm](http://www.AlexionOneSource.com/CoPayForm).

**Submit form to OneSource**

Have patients review and sign the completed form, then fax the completed form to OneSource at 1-800-420-5150 or email to OneSource@Alexion.com.

**Receive CoPay ID number from OneSource**

You will receive communication from OneSource containing the CoPay ID number.

**Provide CoPay ID number to site of care**

Contact OneSource at 1-888-765-4747 or via email at OneSource@Alexion.com.

**IMPORTANT NOTICE:** The Alexion OneSource™ CoPay Program (“Program”) pays for eligible out-of-pocket medication and infusion costs associated with Soliris® (eculizumab) up to $15,000 US dollars per calendar year. The Program is not valid for costs eligible to be reimbursed, in whole or in part, by Medicaid, Medicare (including Medicare Part D), Medicare Advantage Plans, Medigap, Veterans Affairs, Department of Defense or TRICARE, or other federal or state programs (including any state prescription drug assistance programs). No claim for reimbursement of any out-of-pocket expense amount covered by the Program may be submitted to any third-party payer, whether public or private. This offer cannot be combined with any other rebate/coupon, free trial, or similar offer. Patients residing in Massachusetts, Michigan, Minnesota, and Rhode Island are eligible for assistance with medication costs, but are not eligible for assistance with infusion costs. Alexion reserves the right to rescind, revoke, or amend this program without notice. By participating in the Program, participants acknowledge that they understand and agree to comply with the complete terms and conditions, available at [www.AlexionOneSource.com/CoPay](http://www.AlexionOneSource.com/CoPay).

Please see Important Safety Information throughout and accompanying full Prescribing Information for Soliris, including Boxed WARNING regarding serious meningococcal infections.

**References:**

FULL 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).

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).

DOSE AND ADMINISTRATION

For intravenous infusion only

PNH Dosage Regimen: (2.2)

aHUS Dosage Regimen: (2.3)

gMG and NMOSD Dosage Regimen: (2.4)

DOSE 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).

• Infusion-Related Reactions: Monitor patients during infusion, interrupt for reactions, and institute appropriate supportive measures (5.3).

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 trials (>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: 11/2020

FULL PRESCRIBING INFORMATION: CONTENTS* 3

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS 4

1 INDICATIONS AND USAGE 5

1.1 Paroxysmal Nocturnal Hemoglobinuria (PNH) 6

1.2 Atypical Hemolytic Uremic Syndrome (aHUS) 6

1.3 Generalized Myasthenia Gravis (gMG) 6

1.4 Neuromyelitis Optica Spectrum Disorder (NMOSD) 6

2 DOSAGE AND ADMINISTRATION 8

2.1 Recommended Vaccination and Prophylaxis 9

2.2 Recommended Dosage Regimen – PNH 9

2.3 Recommended Dosage Regimen – aHUS 10

2.4 Recommended Dosage Regimen – gMG and NMOSD 10

2.5 Dose Adjustment in Case of Plasmapheresis, Plasma Exchange, or Fresh Frozen Plasma Infusion 11

2.6 Preparation 11

2.7 Administration 11

3 DOSAGE FORMS AND STRENGTHS 12

4 CONTRAINDICATIONS 12

5 WARNINGS AND PRECAUTIONS 13

5.1 Serious Meningococcal Infections 13

5.2 Other Infections 13

5.3 Monitoring Disease Manifestations after Soliris Discontinuation 13

5.4 Thrombosis Prevention and Management 14

5.5 Infusion-Related Reactions 14

6 ADVERSE REACTIONS 15

6.1 Clinical Trial Experience 15

6.2 Immunogenicity 15

6.3 Postmarketing Experience 15

7 USE IN SPECIFIC POPULATIONS 16

8.1 Pregnancy 16

8.2 Lactation 16

8.4 Pediatric Use 16

8.5 Geriatric Use 16

17 PATIENT COUNSELING INFORMATION 17

*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 (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 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 aHUS who are anti-aquaporin-4 (AQP4) antibody positive (1.4).

Soliris is 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 (1.3).

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

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 (1.4).

14.3 Generalized Myasthenia Gravis (gMG)

14.4 Neuromyelitis Optica Spectrum Disorder (NMOSD)

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.
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>
<thead>
<tr>
<th>Patient Body Weight</th>
<th>Induction</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 kg and over</td>
<td>900 mg weekly x 4 doses</td>
<td>1200 mg at week 5; then 1200 mg every 2 weeks</td>
</tr>
<tr>
<td>30 kg to less than 40 kg</td>
<td>600 mg weekly x 2 doses</td>
<td>900 mg at week 3; then 900 mg every 2 weeks</td>
</tr>
<tr>
<td>20 kg to less than 30 kg</td>
<td>600 mg weekly x 2 doses</td>
<td>600 mg at week 3; then 600 mg every 2 weeks</td>
</tr>
<tr>
<td>10 kg to less than 20 kg</td>
<td>600 mg weekly x 1 dose</td>
<td>300 mg at week 2; then 300 mg every 2 weeks</td>
</tr>
<tr>
<td>5 kg to less than 10 kg</td>
<td>300 mg weekly x 1 dose</td>
<td>300 mg at week 2; then 300 mg every 3 weeks</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Type of Plasma Intervention</th>
<th>Most Recent Soliris Dose</th>
<th>Supplemental Soliris Dose With Each Plasma Intervention</th>
<th>Timing of Supplemental Soliris Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasmapheresis or plasma exchange</td>
<td>300 mg</td>
<td>300 mg per each plasmapheresis or plasma exchange session</td>
<td>Within 60 minutes after each plasmapheresis or plasma exchange</td>
</tr>
<tr>
<td></td>
<td>≥600 mg</td>
<td>600 mg per each plasmapheresis or plasma exchange session</td>
<td></td>
</tr>
<tr>
<td>Fresh frozen plasma infusion</td>
<td>≥300 mg</td>
<td>300 mg per infusion of fresh frozen plasma</td>
<td>60 minutes prior to each infusion of fresh frozen plasma</td>
</tr>
</tbody>
</table>

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.

To Dilute Soliris to a final concentration of 5 mg/mL, add 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>
<thead>
<tr>
<th>Soliris Dose</th>
<th>Diluent Volume</th>
<th>Final Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg</td>
<td>30 mL</td>
<td>60 mL</td>
</tr>
<tr>
<td>600 mg</td>
<td>60 mL</td>
<td>120 mL</td>
</tr>
<tr>
<td>900 mg</td>
<td>90 mL</td>
<td>180 mL</td>
</tr>
<tr>
<td>1200 mg</td>
<td>120 mL</td>
<td>240 mL</td>
</tr>
</tbody>
</table>

Immediately 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° to 25° C, 64° to 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° to 8° C (36° to 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-related reaction.

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

3.1 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 (septicaemia 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 for 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.

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). Aspergillus lung abscess and bronchiectasis have been reported for patients treated with Soliris 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

5.3.1 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 reintroduced 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:

A decline 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 or serum bilirubin; an increase in serum LDH by 25% or more over baseline during Soliris treatment; or, an increase in serum LDH by 25% or more over baseline during Soliris treatment.

If TMA complications occur after Soliris discontinuation, consider reinstatement 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-Related Reactions
Administration of Soliris may result in infusion-related reactions, including anaphylaxis or other hypersensitivity reactions. In clinical trials, no patients experienced an infusion-related 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-Related 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 18-86, 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>
<thead>
<tr>
<th>Reaction</th>
<th>Soliris (N=43)</th>
<th>Placebo (N=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>19 (44)</td>
<td>12 (27)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>10 (23)</td>
<td>8 (18)</td>
</tr>
<tr>
<td>Back pain</td>
<td>8 (19)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (16)</td>
<td>11 (26)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (12)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Cough</td>
<td>5 (12)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Herpes simplex infections</td>
<td>3 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>3 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory tract infection</td>
<td>3 (7)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>3 (7)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3 (7)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>3 (7)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>2 (5)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

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 (22%), head (22%), anemia (2), and pyrexia (2%).

aHUS

The safety of Soliris therapy in patients with aHUS has been evaluated in four prospective, single-arm studies, aHUS disease manifestations after Soliris Discontinuation [see Warnings and Precautions (5.3)]. 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 (22%), 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: 1-67 weeks).

Table 5 summarizes all adverse events reported in at least 10% of patients enrolled in Study C08-003A/B and C10-004 combined.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>C08-002A/B (N=17)</th>
<th>C08-003A/B (N=20)</th>
<th>C10-004 (N=41)</th>
<th>Total (N=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (59)</td>
<td>9 (45)</td>
<td>7 (17)</td>
<td>26 (33)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2 (12)</td>
<td>4 (20)</td>
<td>7 (17)</td>
<td>13 (17)</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>3 (18)</td>
<td>2 (10)</td>
<td>4 (10)</td>
<td>9 (12)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>3 (18)</td>
<td>11 (55)</td>
<td>7 (17)</td>
<td>21 (27)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>3 (18)</td>
<td>4 (20)</td>
<td>2 (6)</td>
<td>9 (12)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>5 (29)</td>
<td>8 (40)</td>
<td>2 (5)</td>
<td>15 (19)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>6 (35)</td>
<td>3 (15)</td>
<td>8 (20)</td>
<td>17 (22)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (27)</td>
<td>8 (40)</td>
<td>12 (30)</td>
<td>29 (37)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (27)</td>
<td>9 (45)</td>
<td>6 (15)</td>
<td>22 (30)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (29)</td>
<td>8 (40)</td>
<td>4 (12)</td>
<td>10 (13)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3 (18)</td>
<td>6 (30)</td>
<td>6 (15)</td>
<td>15 (19)</td>
</tr>
</tbody>
</table>

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 other 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 C08-003A/B (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.
and at a greater frequency than on placebo.

In a 26-week placebo-controlled trial evaluating the effect of Soliris for the treatment of gMG (gMG Study Generalized Myasthenia Gravis (gMG)

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

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Soliris (N=96)</th>
<th>Placebo (N=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>5 (8)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (7)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>4 (7)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>2 (40)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>3 (60)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>2 (40)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>2 (40)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>2 (40)</td>
<td>2 (20)</td>
</tr>
</tbody>
</table>

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, constipation, and abdominal pain.

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

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Soliris (N=96)</th>
<th>Placebo (N=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>5 (8)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (7)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>4 (7)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>9 (15)</td>
<td>5 (8)</td>
</tr>
</tbody>
</table>

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 (14.3)]. Patients were 19 to 79 years of age, and 66% 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

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Soliris (N=96)</th>
<th>Placebo (N=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>5 (9)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>5 (8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>6 (6)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>15 (16)</td>
<td>7 (15)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>5 (9)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

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.

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, constipation, and abdominal pain.

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

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Soliris (N=96)</th>
<th>Placebo (N=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>5 (8)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (7)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>4 (7)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>9 (15)</td>
<td>5 (8)</td>
</tr>
</tbody>
</table>

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, constipation, and abdominal pain.

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

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Soliris (N=96)</th>
<th>Placebo (N=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>5 (9)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>5 (8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>6 (6)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>15 (16)</td>
<td>7 (15)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>5 (9)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

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.

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, constipation, and abdominal pain.

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

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Soliris (N=96)</th>
<th>Placebo (N=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>5 (8)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (7)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>4 (7)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>9 (15)</td>
<td>5 (8)</td>
</tr>
</tbody>
</table>

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, constipation, and abdominal pain.

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

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Soliris (N=96)</th>
<th>Placebo (N=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>5 (9)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>5 (8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>6 (6)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>15 (16)</td>
<td>7 (15)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>5 (9)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>
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 IgG2A, 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 contains sodium hydroxide and/or hydrochloric acid to adjust the pH.

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 it 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 it 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 ± 1304 U/L (mean ± SD) at baseline to 700 ± 385 U/L by week one and maintained the effect through the end of the study at week 26 (237 ± 433 U/L) in patients with PNH. In the double-blind 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 eculizumab maximum concentration (Cmax) was 194 ± 76 mcg/mL and the trough concentration (Ctrough) 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 Cmax 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 Cmax was 242 ± 101 mcg/mL. Following intravenous maintenance doses of 1200 mg once every 2 weeks in patients with NMOSD, at week 24, the observed mean ± SD Cmax was 877 ± 331 and the Ctrough was 429 ± 188 mcg/mL.

Serum eculizumab concentration was measured at each week of the starting eculizumab treatment; the accumulation rate was 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 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)].
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 NCT00844846), C08-003A/B (NCT00835851 and NCT00844498), C010-003 (NCT01193348), and C010-004 (NCT01194973); and one retrospective: C09-001r (NCT01770951)] evaluated the safety and efficacy of Soliris for the treatment of aHUS. Patients with aHUS received meningoococcal 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 infusional, and new dialysis requirement)
- Daily TMA intervention rate (defined as the number of plasma exchange or plasma infusional interventions and the number of new dialyses required per patient per day).

Efficacy evaluations were based on thrombotic microangiopathy (TMA) endpoints.

Soliris 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 x109/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 26 (range: 17 to 52 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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study C08-002A/B (N=17)</th>
<th>Study C08-002A/B at 2 yrs* (N=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from aHUS diagnosis until screening in months, median (min, max)</td>
<td>10 (6.26, 23.6)</td>
<td>10 (0.26, 23.6)</td>
</tr>
<tr>
<td>Time from current clinical TMA manifestation until screening in months, median (min, max)</td>
<td>&lt;1 (-1, 4)</td>
<td>&lt;1 (-1, 4)</td>
</tr>
<tr>
<td>Baseline platelet count (x10^9/L), median (range)</td>
<td>118 (62, 261)</td>
<td>118 (62, 261)</td>
</tr>
<tr>
<td>Baseline LDH (UL, median (range)</td>
<td>269 (134, 634)</td>
<td>269 (134, 634)</td>
</tr>
</tbody>
</table>

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).

Weekly moderate dose Conclusions about efficiency and interpretation should be made with caution. The 26-week median duration of treatment was 26 weeks, six additional patients achieved Complete TMA response. Twenty-six percent of patients achieved Complete TMA response, 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 213 ± 70 x109/L at baseline, and was maintained through 26 weeks (37 ± 21 x109/L and 24 weeks (40 ± 18 x109/L). 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 x109/L at baseline, 233 ± 69 x109/L at week 26, and 224 ± 52 x109/L at 2 years. When treatment was continued for more than 54 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

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Study C08-003A/B at 26 wks† (N=20)</th>
<th>Study C08-003A/B at 2 yrs‡ (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete TMA response, n (%)</td>
<td>5 (25)</td>
<td>11 (55)</td>
</tr>
<tr>
<td>Median duration of complete TMA response, weeks (range)</td>
<td>32 (12, 38)</td>
<td>68 (38, 109)</td>
</tr>
<tr>
<td>eGFR improvement ≥15 mL/min/1.73 m2, n (%)</td>
<td>1 (5)</td>
<td>8 (40)</td>
</tr>
<tr>
<td>TMA Event-free status n (%)</td>
<td>16 (80)</td>
<td>19 (95)</td>
</tr>
<tr>
<td>Daily TMA intervention rate, median (range) Before eculizumab</td>
<td>0.23 (0.5, 1.07)</td>
<td>0.23 (0.5, 1.07)</td>
</tr>
<tr>
<td>On eculizumab treatment</td>
<td>0</td>
<td>0 (0, 0.01)</td>
</tr>
<tr>
<td>Hematologic normalization, n (%)</td>
<td>18 (90)</td>
<td>18 (90)</td>
</tr>
<tr>
<td>Median duration of hematologic normalization, weeks (range)</td>
<td>38 (22, 52)</td>
<td>114 (33, 125)</td>
</tr>
</tbody>
</table>

1. At data cut-off (September 8, 2010).
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 (Study C09-001r)

The efficacy results for the aHUS retrospective study (Study C09-001r) were generally consistent with the 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 217 ± 31 x109/L at week 1 to 233 ± 108 x109/L after one week of therapy; this effect was maintained through 26 weeks (mean platelet count (± SD) at week 26: 254 ± 79 x109/L). A total of 19 pediatric patients (ages 2 months to 17 years) received Soliris in Study C09-001r. The median duration of treatment 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

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>&lt;2 yrs (N=5)</th>
<th>2 to &lt;12 yrs (N=10)</th>
<th>12 to &lt;18 yrs (N=4)</th>
<th>Total (N=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete TMA response, n (%)</td>
<td>2 (40)</td>
<td>5 (50)</td>
<td>1 (25)</td>
<td>8 (42)</td>
</tr>
<tr>
<td>Patients with eGFR improvement ≥15 mL/min/1.73 m2, n (%)</td>
<td>2 (40)</td>
<td>6 (60)</td>
<td>1 (25)</td>
<td>9 (47)</td>
</tr>
<tr>
<td>Platelet count normalization, n (%)</td>
<td>4 (80)</td>
<td>10 (100)</td>
<td>3 (75)</td>
<td>17 (89)</td>
</tr>
<tr>
<td>Hematologic normalization, n (%)</td>
<td>2 (40)</td>
<td>5 (50)</td>
<td>1 (25)</td>
<td>8 (42)</td>
</tr>
<tr>
<td>Daily TMA intervention rate, median (range) Before eculizumab</td>
<td>1 (0, 2)</td>
<td>&lt;1 (0, 1)</td>
<td>&lt;1 (0, 0.7)</td>
<td>&lt;1 (0, 0.7)</td>
</tr>
<tr>
<td>On eculizumab treatment</td>
<td>0 (0, 0.31)</td>
<td>0 (0, 0.31)</td>
<td>0 (0, 0.31)</td>
<td>0 (0, 0.31)</td>
</tr>
</tbody>
</table>
1. Platelet count normalization was defined as a platelet count of at least 150,000 X10^9/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 m2, 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 trials 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/P before eculizumab.

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study C10-004 (N=41)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from aHUS diagnosis until start of study drug in months, median (range)</td>
<td>0.79 (0.03 – 311)</td>
<td>0.20 (0.03-4)</td>
</tr>
<tr>
<td>Time from current clinical TMA manifestation until first study dose in months, median (range)</td>
<td>0.02 (0.03-19)</td>
<td>0.00 (0.00-1)</td>
</tr>
<tr>
<td>Baseline platelet count (&lt; 10^11/L), median (range)</td>
<td>125 (6-332)</td>
<td></td>
</tr>
<tr>
<td>Baseline LDH (U/L), median (range)</td>
<td>375 (131-3318)</td>
<td></td>
</tr>
</tbody>
</table>

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 ± 60 x10^11/L at baseline to 202 ± 84 x10^11/L by one week; this effect was maintained through 26 weeks (mean platelet count (± SD) at week 26: 252 ± 70 x10^11/L). 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: Efficacy Results for Study C10-004

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Study C10-004 (N=41)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete TMA response, n (%)</td>
<td>23 (56)</td>
<td>0.006 (a); 0.014 (b)</td>
</tr>
<tr>
<td>95% CI</td>
<td>40,72</td>
<td></td>
</tr>
<tr>
<td>Median duration of complete TMA response, weeks (range)</td>
<td>42.0 (6.75)</td>
<td></td>
</tr>
<tr>
<td>Patients with eGFR improvement ≥ 15 mL/min/1.73m^2, n (%)</td>
<td>22 (54)</td>
<td></td>
</tr>
<tr>
<td>Hematologic Normalization, n (%)</td>
<td>36 (88)</td>
<td></td>
</tr>
<tr>
<td>Median duration of hematologic normalization, weeks (range)</td>
<td>46.1 (10.75)</td>
<td></td>
</tr>
<tr>
<td>TMA Event-Free Status, n (%)</td>
<td>37 (90)</td>
<td></td>
</tr>
<tr>
<td>Daily TMA Intervention Rate, median (range)</td>
<td>0.83 (0, 1.38)</td>
<td></td>
</tr>
<tr>
<td>Before eculizumab</td>
<td>0.00 (0, 0.58)</td>
<td></td>
</tr>
<tr>
<td>On eculizumab treatment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 ≥37 percent for age with the need for chronic dialysis. The median patient age was 6.5 (range: 1.6 to 17.5) 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/P 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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients 1 month to &lt;12 years (N=18)</th>
<th>All Patients (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from aHUS diagnosis until start of study drug in months, median (range)</td>
<td>0.51 (0.03 – 58)</td>
<td>0.56 (0.03-191)</td>
</tr>
<tr>
<td>Time from current clinical TMA manifestation until first study dose in months, median (range)</td>
<td>0.23 (0.03 – 4)</td>
<td>0.2 (0.03-4)</td>
</tr>
<tr>
<td>Baseline platelet count (&lt; 10^11/L), median (range)</td>
<td>110 (19-146)</td>
<td>91 (19-146)</td>
</tr>
<tr>
<td>Baseline LDH (U/L), median (range)</td>
<td>1510 (232-7164)</td>
<td>1244 (232-7164)</td>
</tr>
</tbody>
</table>

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 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 of ≥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 x10^11/L at baseline to 291 ± 123 x10^11/L by one week; this effect was maintained through 26 weeks (mean platelet count (± SD) at week 26: 293 ± 106 x10^11/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.
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 IVlg 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

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Statistic</th>
<th>Placebo (N = 47)</th>
<th>Soliris (N = 96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of relapses</td>
<td>Sum</td>
<td>21</td>
<td>3</td>
</tr>
<tr>
<td>Adjusted adjudicated ARRa</td>
<td>Rate</td>
<td>0.350</td>
<td>0.016</td>
</tr>
<tr>
<td>Treatment effect</td>
<td>Rate ratio (eculizumab/placebo)</td>
<td>...</td>
<td>0.045</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>...</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

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 2°-8° C (36°-46° 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 (6.1)].

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
- severe headache with stiff neck or stiff back
- fever
- muscle aches with flu-like symptoms
- eyes sensitive to light

Inform patients that if they are 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.

Infusion-Related Reactions

Advise patients that administration of SOLIRIS may result in infusion-related reactions.

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

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 Haemophilus influenzae type b (Hib). Certain people may be at risk for 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).

• 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 infusion-related 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 infusion-related 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
• 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 infusion-related reactions.** Serious infusion-related 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 infusion-related 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

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 Revised: 11/2020