Helpful information on the required vaccinations your patients need throughout treatment with Soliris

INDICATIONS

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.

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.

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.

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 additional Important Safety Information throughout and accompanying full Prescribing Information for Soliris, including Boxed WARNING regarding serious meningococcal infections.
Meningococcal vaccinations and Soliris: What you need to know

Vaccinations are an important part of treatment with Soliris® (eculizumab)

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).

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

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

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). 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 additional Important Safety Information throughout and accompanying full Prescribing Information for Soliris, including Boxed WARNING regarding serious meningococcal infections.
Immunize patients with both types of meningococcal vaccines at least 2 weeks before starting treatment with Soliris\textsuperscript{1,2}

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.\textsuperscript{3}

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Dosage</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>MenACWY</td>
<td>2 doses</td>
<td>At least 8 weeks apart</td>
</tr>
<tr>
<td>MenB-4C</td>
<td>2 doses</td>
<td>At least 1 month apart</td>
</tr>
<tr>
<td>MenB-FHbp</td>
<td>3 doses</td>
<td>0, 1-2, and 6 months\textsuperscript{b}</td>
</tr>
</tbody>
</table>

Revaccinate every 5 years\textsuperscript{a} if risk remains for MenACWY and MenB-FHbp.

\textsuperscript{a}The Centers for Disease Control and Prevention ACIP guidelines recommend all patients undergoing complement inhibition receive the MenACWY booster every 5 years.

\textsuperscript{b}For MenB-FHbp, if dose 2 was administered at least 6 months after dose 1, dose 3 is not needed.

\textsuperscript{c}Special situations for MenB include those receiving a complement inhibitor (eg, eculizumab). ACIP recommends a MenB booster dose 1 year following completion of a MenB primary series followed by MenB booster doses every 2 to 3 years if risk remains.

Vaccinate for meningococcal disease according to the most current ACIP recommendations for patients with complement deficiencies and for patients receiving a complement inhibitor. 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 2 weeks of antibacterial drug prophylaxis.

The benefits and risks of antibiotic prophylaxis for prevention of meningococcal infections in patients receiving Soliris have not been established.

Please see the respective meningococcal vaccine Prescribing Information for complete details, including vaccine Warnings, Precautions, and Contraindications.

- If your patient received meningococcal vaccines in the past, they might need additional vaccination before starting Soliris.
- The choice of vaccine deemed medically appropriate is your independent decision.
- In most cases, your patients can receive meningococcal vaccines at a physician’s office or retail pharmacy.
- MenACWY and MenB vaccines may be administered during the same visit but at different injection sites.
- To help reduce the risk of meningococcal infection, the complete series for the MenACWY and MenB vaccines should be administered. Booster doses for the MenACWY vaccines are currently recommended every 5 years if a patient remains on Soliris. Booster doses for the MenB vaccines are recommended 1 year following completion of the series and every 2 to 3 years if risk remains.

Access the latest adult vaccination recommendations from ACIP by visiting [CDC.gov/vaccines/schedules/hcp/imz/adult.html](https://CDC.gov/vaccines/schedules/hcp/imz/adult.html).
Additional steps required to start your patients on Soliris

1. Enroll in the Soliris® (eculizumab) Risk Evaluation and Mitigation Strategy (REMS) program

Because of the risk of meningococcal infections, Soliris is available only through a restricted program under a 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).

2. Give your patients a Patient Safety Card and instruct them to carry it at all times

This card identifies the signs and symptoms of meningococcal infection and advises patients to seek immediate medical attention if these signs or symptoms occur.

Contact your Soliris representative for additional information on starting adult patients on Soliris.

SELECT IMPORTANT SAFETY INFORMATION

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).

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.

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.

Adverse Reactions
The most frequently reported adverse reaction in the 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 additional Important Safety Information throughout and accompanying full Prescribing Information for Soliris, including Boxed WARNING regarding serious meningococcal infections.

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 (STE-C-HUS).
- The treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive (1.4).
- The treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive (1.4).

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 (#HUS) 6
1.3 Generalized Myasthenia Gravis (gMG) 6
1.4 Neuromyelitis Optica Spectrum Disorder (NMOSD) 6
2 DOSAGE AND ADMINISTRATION 7
2.1 Recommended Vaccination and Prophylaxis 7
2.2 Recommended Dosage Regimen – PNH 7
2.3 Recommended Dosage Regimen – aHUS 7
2.4 Recommended Dosage Regimen – gMG and NMOSD 8
2.5 Dose Adjustment in Case of Plasmapheresis, Plasma Exchange, or Fresh Frozen Plasma Infusion 8
2.6 Preparation 8
2.7 Administration 8

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 (5.5).

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 clinical 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: 11/2020

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 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.

1.3 Generalized Myasthenia Gravis (gMG)
Soliris is indicated for the treatment of generalized myasthenia gravis in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.

1.4 Neuromyelitis Optica Spectrum Disorder (NMOSD)
Soliris is indicated for the treatment of neuromyelitis optica spectrum disorder 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)).

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...
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>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 NMOSS
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 NMOSS, supplemental dosing of Soliris is required in the setting of concomitant plasmapheresis or plasma exchange, or fresh frozen plasma infusion (PE/PFI) (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>≥600 mg</td>
<td>600 mg per each plasmapheresis or plasma exchange session</td>
<td></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.
- 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>
<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>

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-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.

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 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).

Vaccination 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 (1-888-766-7675) 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). Hib vaccine variances 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 reinstated 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:

- An increase in serum lactate dehydrogenase (LDH) by 25% or more over baseline or nadir during Soliris treatment.
- The 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 reinstatement of Soliris treatment, plasma therapy [plasmapheresis, plasma exchange, or fresh frozen plasma infusion (PE/PFI)], 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 18-85, 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

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Soliris (N=17)</th>
<th>Placebo (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>19 (44)</td>
<td>12 (27)</td>
</tr>
<tr>
<td>N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (16)</td>
<td>5 (11)</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>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 in 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: 2-143 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

<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>Nephropathy</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>8 (47)</td>
<td>8 (40)</td>
<td>12 (30)</td>
<td>29 (37)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8 (47)</td>
<td>9 (45)</td>
<td>6 (15)</td>
<td>23 (30)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (29)</td>
<td>8 (40)</td>
<td>5 (12)</td>
<td>18 (23)</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 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 8: Adverse Reactions Reported in 5% or More of Soliris-Treated Patients in gMG Study 1 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 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 7: Adverse Reactions Occurring in at Least 15% of Patients Less than 18 Years of Age

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 91% were female. Table 9 displays the most common adverse reactions that occurred in ≥10% of Soliris-treated patients in the long-term extension to gMG Study 1, Study ECL-MG-302, and that were not included in Table 8. 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.

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.

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 is risk 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. When maternal exposure to the antibody occurred during organogenesis, two cases of renal 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 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 renal 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
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 446 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 0.6 mg/mL polysorbate 80 (0.6 mg/g of eculizumab), sodium chloride (263.1 mg/mL), sodium phosphate dibasic (53.4 mg/mL), sodium phosphate monobasic (13.8 mg/mL), and Water for Injection, USP.

### 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 PNH patients is unknown, but is presumed to involve reduction of terminal complement complex C5b-9 deposition at the neutrophil membrane.

The precise mechanism by which eculizumab exerts its therapeutic effect in aHUS 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 ± 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 second 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 (Cmax) was 194 ± 76 mcg/mL and the trough concentration (Ctrough) was 97 ± 36 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 273 ± 283 mcg/mL and the Ctrough was 172 ± 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 Cmax was 877 ± 331 and the Ctrough was 429 ± 188 mcg/mL.

Soliris was administered every 2 weeks 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 to 2.6 h. Supplemental dosing is recommended when Soliris is administered to patients receiving plasma exchange or infusion [see Dosage and Administration (2.5)].
4.2 Atypical Hemolytic Uremic Syndrome (aHUS)

Five single-arm studies [four prospective: C08-002A/B (NCT00844454 and NCT00844446), C08-003A/B (NCT00385513 and NCT00384449), C08-003A/B (NCT01193548), C08-003A/B (NCT01199473); 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 to 2 days for 4 weeks, followed by 1200 mg every 7 to 2 days thereafter, then 1200 mg every 14 to 2 days thereafter. The dosage regimen for pediatric patients weighing less than 40 kg enrolled in Study C09-001r and Study C010-003 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 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 thrombocytopenia which (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 years (range: 13 to 63 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 C08-003A/B at 2 yrs (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from aHUS diagnosis until screening, months, median (min, max)</td>
<td>10 (0.26, 236)</td>
<td>16 (0.82, 254)</td>
</tr>
<tr>
<td>Time from current clinical TMA manifestation until screening, months, median (min, max)</td>
<td>&lt;1 (&lt;, 4)</td>
<td>0 (0, 0.01)</td>
</tr>
<tr>
<td>Baseline platelet count (&lt; 10^11/L), median (range)</td>
<td>118 (62, 261)</td>
<td>15 (5)</td>
</tr>
<tr>
<td>Baseline LDH (UL), median (range)</td>
<td>269 (134, 634)</td>
<td>68 (38, 109)</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).

Renal function, as measured by eGFR, 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. 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 C08-002A/B, responses to Soliris were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins.

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

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Study C08-002A/B at 26 wks (N=17)</th>
<th>Study C08-003A/B at 2 yrs (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete TMA response, n (%)</td>
<td>11 (65)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Median duration of complete TMA response, weeks (range)</td>
<td>13 (77)</td>
<td>18 (90)</td>
</tr>
<tr>
<td>eGFR improvement ≥15 mL/min/1.73 m^2, n (%)</td>
<td>9 (53)</td>
<td>32 (12, 38)</td>
</tr>
<tr>
<td>Median duration of eGFR improvement, days (range)</td>
<td>251 (70, 392)</td>
<td>38 (22, 52)</td>
</tr>
<tr>
<td>Hematologic normalization, n (%)</td>
<td>13 (76)</td>
<td>114 (33, 125)</td>
</tr>
<tr>
<td>Median duration of hematologic normalization, weeks (range)</td>
<td>37 (25, 62)</td>
<td>15 (88)</td>
</tr>
<tr>
<td>TMA event-free status, n (%)</td>
<td>15 (88)</td>
<td>15 (88)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study C08-003A/B (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Duration of hematologic normalization, weeks</td>
<td>37 (25, 62)</td>
</tr>
<tr>
<td>Complete TMA response, n (%)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Median duration of complete TMA response, weeks (range)</td>
<td>32 (12, 38)</td>
</tr>
<tr>
<td>eGFR improvement ≥15 mL/min/1.73 m^2, n (%)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Median duration of hematologic normalization, weeks (range)</td>
<td>38 (22, 52)</td>
</tr>
<tr>
<td>TMA Event-free status, n (%)</td>
<td>16 (80)</td>
</tr>
</tbody>
</table>

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=10)</th>
<th>Study C08-003A/B at 2 yrs (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete TMA response, n (%)</td>
<td>2 (20)</td>
<td>8 (40)</td>
</tr>
<tr>
<td>Median duration of complete TMA response, weeks (range)</td>
<td>32 (12, 38)</td>
<td>38 (22, 52)</td>
</tr>
<tr>
<td>eGFR improvement ≥15 mL/min/1.73 m^2, n (%)</td>
<td>0 (0, 0.01)</td>
<td>0 (0, 0.01)</td>
</tr>
<tr>
<td>Hematologic normalization, n (%)</td>
<td>18 (90)</td>
<td>114 (33, 125)</td>
</tr>
<tr>
<td>Median duration of hematologic normalization, weeks (range)</td>
<td>18 (90)</td>
<td>38 (22, 52)</td>
</tr>
</tbody>
</table>

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

1 At data cut-off (April 20, 2012).

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 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 171 ± 83 x 10^9/L after one week of therapy, this effect was maintained through 26 weeks (mean platelet count (± SD) at week 26: 254 ± 79 x 10^9/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 36 weeks (range 1 to 69 weeks) for patients 12 to <18 years of age (n=6). 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 17: Baseline Characteristics of Patients Enrolled in Study C10-004

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study C10-004 (N=41)</th>
<th>Study C10-003 (N=21)</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>0.52 (0.03-19)</td>
</tr>
<tr>
<td>Baseline platelet count (x 10^9/L), median (range)</td>
<td>125 (16 – 332)</td>
<td>125 (16 – 332)</td>
</tr>
<tr>
<td>Baseline LDH (U/L), median (range)</td>
<td>375 (131 – 3318)</td>
<td>375 (131 – 3318)</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-six 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 ± 90 x10^10/L at baseline to 252 ± 70 x10^10/L by week 26; mean platelet count (± SD) increased from 125 ± 87 x10^10/L at baseline to 269 ± 106 x10^10/L by week 26. Patients enrolled 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: Efficacy Results for Study C10-004

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Study C10-004 (N=41)</th>
<th>Study C10-003 (N=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete TMA response, n (%), 95% CI</td>
<td>23 (56) [0.63 (0, 1.38)]</td>
<td>20 (95) [0.4 (0, 1.7)]</td>
</tr>
<tr>
<td>Reduction in terminal complement activity</td>
<td>37 (90) [0.0 (0, 0.01)]</td>
<td>37 (90) [0.0 (0, 0.01)]</td>
</tr>
<tr>
<td>Daily TMA Intervention Rate, median (range)</td>
<td>Before eculizumab 0.63 (0, 1.38)</td>
<td>Before eculizumab 0.2 (0, 0.58)</td>
</tr>
<tr>
<td>On eculizumab treatment</td>
<td>0.0 (0, 0.58)</td>
<td>0.0 (0, 0.58)</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, 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 this trial was 26%-116%. Fifty-one percent of patients had an identified complement regulatory factor mutation or auto-antibody. A total of 35 patients received PE/PRI prior to eculizumab. Table 17 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in Study C10-004.

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 (x 10^9/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 (382-7164)</td>
<td>1244 (382-7164)</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 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 x10^10/L at baseline to 261 ± 123 x10^10/L by one week; this effect was maintained through 26 weeks (mean platelet count ± SD) at week 26: 293 ± 106 x10^10/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 IFN 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% 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).

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).

**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 medication. 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**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (N = 47)</th>
<th>Soliris (N = 96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of relapses</td>
<td>Sum 21</td>
<td>3</td>
</tr>
<tr>
<td>Adjusted adjudicated ARR*</td>
<td>Rate 0.350</td>
<td>0.016</td>
</tr>
<tr>
<td>Treatment effect*</td>
<td>Rate ratio (eculizumab/placebo) ... 0.045</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p-value &lt;0.0001</td>
<td></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 (2.4) 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 vaccine 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 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 influenza type b (Hib) according to current medical guidelines.

Infection-Related Reactions

Advise patients that administration of SOLIRIS may result in infection-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.

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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
   - 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 (aspergillosis) 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 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:
  o weekly for five weeks, then
  o 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.
• 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 cloting (thrombotic microangiopathy).

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:
  o chest pain
  o trouble breathing or shortness of breath
  o swelling of your face, tongue, or throat
  o 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)

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

• 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)

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)
• joint pain (arthritis)
• 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

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