In pediatric patients with aHUS, inhibit complement-mediated thrombotic microangiopathy (TMA) with Soliris® (eculizumab)\textsuperscript{1}

Please see pages 15-16 for Important Safety Information.

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

US/SOL-a/0030

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

Limitation of Use
Soliris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).
**Soliris® (eculizumab) Select Important Safety Information**

**IMPORTANT SAFETY 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.

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

**Soliris® (eculizumab) specifically inhibits chronic, uncontrolled complement activity, which causes the signs and TMA manifestations of aHUS**

- Soliris binds C5 to block terminal complement activity.
- **Soliris** binds C5 to block terminal complement activity.

- **Mechanism of action**
  - Soliris binds C5 to block terminal complement activity.
  - **Soliris** binds C5 to block terminal complement activity.

- **Consequences**
  - Anaphylaxis
  - Inflammation
  - Thrombosis
  - Hemolysis
  - Inflammation
  - Thrombosis
  - Tissue damage

- **Immune response of the proximal pathway remains intact**

Please see pages 15-16 for additional Important Safety Information.

Please see accompanying full Prescribing Information for Soliris, including Boxed WARNING regarding serious meningococcal infections.
First prospective non-randomized phase II clinical trial of Soliris® (eculizumab) in pediatric patients with aHUS\(^\text{1,5}\)

- Open-label, single-arm, multicenter multinational clinical trial\(^\text{1,5}\)

### Study design\(^\text{1,5}\)

#### Key inclusion criteria
- Age 1 month to <18 years with a body weight ≥5 kg
- Platelet count < Lower limit of normal range (LLN)
- Signs or symptoms of hemolysis
  - Lactate dehydrogenase (LDH) ≥1.5 × Upper limit of normal range (ULN)
  - Hemoglobin ≤ LLN
  - Fragmented red blood cells with a negative Coombs test
- Serum creatinine (Scr) ≥97th percentile for age without the need for chronic dialysis
- No requirement for identified complement mutation or antibody
- ADAMTS13 activity >5%

#### Key exclusion criteria
- Chronic dialysis
- Shiga toxin–producing \(E.\) coli (STEC-HUS) infection
- Therapeutic plasma exchange/plasma infusion (TPE/PI) for >5 weeks

#### Primary end point
- Proportion of patients who achieved complete TMA response during 26 weeks\(^*\)

#### Secondary end points
- Safety and tolerability
- Hematologic normalization\(^1\)
- TMA event-free status
  - No decrease in platelet count by greater than 25% from baseline
  - No TPE/PI
  - No new dialysis
- Recovery of kidney function\(^1\)
- Change in health-related quality of life

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13.

\(^{\text{1}}\)Complete TMA response defined as platelet count ≥150 × 10^9/L, LDH < ULN, and ≥25% improvement in Scr. All 3 parameters had to be met on 2 consecutive measurements obtained ≥4 weeks apart.\(^{\text{2}}\)

\(^{\text{2}}\)Hematologic normalization defined as platelet count ≥150 × 10^9/L and LDH < ULN sustained for ≥2 consecutive measurements obtained ≥4 weeks apart.\(^{\text{2}}\)

\(^{\text{3}}\)eGFR was calculated using the Schwartz formula: eGFR (mL/min/1.73 m^2) = \(0.413 \times \text{height} \text{(cm)}/\text{Scr (mg/dL)}\).\(^{\text{2}}\)

### Patients exhibited a broad range of baseline characteristics\(^1,5\)

#### Select demographic and baseline laboratory values\(^1,5\)

<table>
<thead>
<tr>
<th>Category</th>
<th>Intent-to-treat population (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients ranged in age from 5 months to 18 years(^*)</td>
<td></td>
</tr>
<tr>
<td>1 month to &lt;23 months, n (%)</td>
<td>5 (23)</td>
</tr>
<tr>
<td>≥23 months to &lt;5 years, n (%)</td>
<td>5 (23)</td>
</tr>
<tr>
<td>≥5 to &lt;12 years, n (%)</td>
<td>8 (36)</td>
</tr>
<tr>
<td>≥12 to &lt;18 years, n (%)</td>
<td>4 (18)</td>
</tr>
<tr>
<td>The majority of patients were newly diagnosed</td>
<td></td>
</tr>
<tr>
<td>First clinical TMA manifestation, n (%)</td>
<td>16 (73)</td>
</tr>
<tr>
<td>50% of patients did not have an identified genetic mutation, n (%)</td>
<td>11 (50)</td>
</tr>
<tr>
<td>27% of patients reported a family history of aHUS, n (%)</td>
<td>6 (27)</td>
</tr>
<tr>
<td>55% of patients did not receive TPE/PI during current manifestation, n (%)</td>
<td>12 (55)</td>
</tr>
<tr>
<td>Patients showed evidence of disease severity</td>
<td></td>
</tr>
<tr>
<td>Platelet count &lt;150 × 10^9/L, n (%)</td>
<td>22 (100)</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m^2), mean (SD)(^{\text{3}})</td>
<td>33 (30)</td>
</tr>
<tr>
<td>Dialysis at baseline, n (%)(^1)</td>
<td>11 (50)</td>
</tr>
<tr>
<td>Prior renal transplant, n (%)</td>
<td>2 (9)</td>
</tr>
</tbody>
</table>

\(^*\)Patients as young as 1 month old were eligible for study inclusion. Median age at first infusion was 6.5 years (range, 0.4 to 17 years).\(^{\text{5}}\)

\(^{\text{4}}\)82% (18/22) of patients at baseline had an eGFR of <60 mL/min/1.73 m^2.\(^{\text{2}}\)

\(^{\text{5}}\)One patient who was on dialysis at baseline discontinued dialysis during the baseline window prior to the first dose of Soliris® (eculizumab).\(^{\text{1}}\)

- Median duration (range) from the onset of the presenting clinical manifestation to first dose was 6 days (0 to 4 months)\(^{1,5}\)
- 19 patients completed the 26-week study period\(^6\)
  - Of the 3 patients who withdrew, 1 patient was diagnosed with STEC-HUS, 1 patient had a serious adverse event (agitation), and 1 patient’s family requested to withdraw

### IMPORTANT SAFETY INFORMATION

#### Contraindications
Soliris is contraindicated in:
- 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 pages 15-16 for additional Important Safety Information.

Please see accompanying full Prescribing Information for Soliris, including Boxed WARNING regarding serious meningococcal infections.
Treatment with Soliris® (eculizumab) resulted in complete TMA response in 64% (95% CI, 41%-83%; 14/22) of pediatric patients with aHUS.

**Complete TMA response was defined by a combination of renal and hematologic end points:5**

- Median time to complete TMA response was 8.6 (range, 1-21.9) weeks.

**Mean improvement in platelet count from baseline**

- All patients had low platelet counts at baseline, characteristic of aHUS (<150 × 10^9/L) with a mean platelet count ± SD of 88 ± 42 × 10^9/L.
- Median time (range) to platelet count normalization was 7 (1-80) days.
- At 27 weeks, the mean improvement in platelet count from baseline was 164 ± 76 × 10^9/L.
- Of the 10 patients receiving TPE/PI at baseline, none required TPE/PI by the end of the 26-week study period.

**Improvements in platelet count were rapid and sustained throughout the study period.**

![Proportion of patients achieving complete TMA response at 26 weeks](image)

- 82% (95% CI, 60%-95%; 18/22) of patients achieved hematologic normalization in a median time of 55 days (range, 1-153 days).
- Median time to complete TMA response was 8.6 (range, 1-21.9) weeks.

**WARNINGs AND PRECAUTIONS**

**Serious Meningococcal Infections**

Risk and Prevention

See Boxed WARNING for additional information on serious meningococcal infections. 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).

Vaccinate for meningococcal disease according to the most current 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 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.

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.

**IMPORTANT SAFETY INFORMATION**

**Adverse Reactions**

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.

Please see pages 15-16 for additional Important Safety Information.

Please see accompanying full Prescribing Information for Soliris, including Boxed WARNING regarding serious meningococcal infections.
Dialysis was eliminated in 82% (9/11) of pediatric patients with aHUS at 26 weeks while on Soliris® (eculizumab) therapy1,5

- Dialysis was eliminated in 9/11 pediatric patients receiving dialysis at study entry while on Soliris therapy1,5
  — All patients not on dialysis at start of treatment remained dialysis free5

In the pediatric study, 85% (17/20) of patients with CKD stage ≥2 at baseline achieved improvement of ≥1 stage within 26 weeks1,5

- Mean increase in eGFR from baseline was 64 mL/min/1.73 m² (P<0.0001)5

**Mean improvement in eGFR**

- 86% (19/22) of patients achieved improvement in renal function1,5
  - Defined as eGFR change ≥15 mL/min/1.73 m² from baseline sustained for ≥2 consecutive measurements obtained ≥4 weeks apart.5

**Warns and Precautions**

**Serious Meningococcal Infections**

**REMS**

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).
Review of safety from prospective trial of Soliris® (eculizumab) in pediatric patients with aHUS

Per-patient incidence of adverse reactions in 10% or more patients enrolled in Study C10-003:

<table>
<thead>
<tr>
<th>Category</th>
<th>Number (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 month to &lt;12 years (n=18)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6 (33)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (28)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>9 (50)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>5 (28)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Catheter site infection</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>7 (39)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (22)</td>
</tr>
</tbody>
</table>

- No deaths or meningococcal infections reported during the study period.
- 59% (13/22) of patients experienced a serious adverse event, the majority of which were mild to moderate in severity.
- The most common adverse events in this study were hypertension (9%), viral gastroenteritis (9%), pyrexia (9%), and upper respiratory tract infections (9%).
- One patient discontinued Soliris due to an adverse event (severe agitation).

Patients who discontinue or deviate from the recommended dosing schedule of Soliris® (eculizumab) are at immediate and ongoing risk of severe complications from TMA:

- Of 18 adult and pediatric patients who discontinued Soliris during the aHUS clinical trials (N=100), 28% (5/18) experienced severe complications from TMA after a missed dose:
  - Of the patients who experienced severe complications from TMA, 40% (2/5) were pediatric patients.
  - 80% (4/5) reinitiated Soliris treatment.

- Monitor patients for signs and symptoms of TMA complications.
  - Changes in mental status, seizures, angina, dyspnea, or thrombosis.

In addition, the following changes in laboratory parameters may identify a TMA complication (occurrence of 2, or repeated measurement of any 1 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 LDH by 25% or more over baseline or nadir during Soliris treatment.
- An increase in serum creatinine by 25% or more compared to baseline or nadir during Soliris treatment.

In patients who discontinue Soliris, clinical and laboratory signs should be monitored for at least 12 weeks.

If TMA complications occur after Soliris discontinuation, consider reinstitution of Soliris treatment, plasma therapy (plasmapheresis, TPE, or fresh frozen P1), or appropriate organ-specific supportive measures.

Please see pages 15-16 for additional Important Safety Information.

Please see accompanying full Prescribing Information for Soliris, including Boxed WARNING regarding serious meningococcal infections.
Soliris® (eculizumab) is approved for use in pediatric patients with aHUS.1

**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**

**Serious Meningococcal Infections**

**Risk and Prevention**

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. The use of Soliris increases a patient's susceptibility to serious meningococcal infections (septicemia and/or meningitis).

Vaccinate for meningococcal disease according to the most current 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 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.

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.

**Other Infections**

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

Soliris blocks terminal complement activation; therefore patients may have increased susceptibility to infections, especially with encapsulated bacteria. Additionally, *Aspergillus* infections have occurred in immunocompromised and neutropenic patients.

Children treated with Soliris may be at increased risk of developing serious infections due to *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib). Administer vaccinations for the prevention of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) infections according to ACIP guidelines. Use caution when administering Soliris to patients with any systemic infection.

**Infusion Reactions**

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

**Dosing**

- **Body weight: 40 kg and over**
  - **Induction phase:** 1 infusion 900 mg q12wk
  - **Maintenance phase:** 2 infusions 300 mg q6wk

- **Body weight: 20 kg to less than 40 kg**
  - **Induction phase:** 1 infusion 600 mg q2wk
  - **Maintenance phase:** 2 infusions 300 mg q6wk

- **Body weight: 10 kg to less than 20 kg**
  - **Induction phase:** 1 infusion 400 mg q2wk
  - **Maintenance phase:** 2 infusions 200 mg q6wk

- **Body weight: 5 kg to less than 10 kg**
  - **Induction phase:** 1 infusion 300 mg q2wk
  - **Maintenance phase:** 2 infusions 300 mg q6wk

**If an adverse reaction occurs during the administration of Soliris, the infusion may be slowed or stopped at the discretion of the physician.1**

**Monitor the patient for at least one hour following completion of the infusion for signs or symptoms of an infusion reaction.**1

*Physicians must read Important Safety Information prior to administering Soliris.*

**Call 1.888.SOLIRIS (1.888.765.4747) to speak with an Alexion Nurse Case Manager**

**“Dealing with a rare disease can be an isolating experience. Patients often feel like they’re alone, but that’s why I’m here. I can hear the relief in their voices when I help with something that’s been troubling them. That’s a good feeling—for them and me.”**

—Alexion Nurse Case Manager

**IMPORTANT SAFETY INFORMATION**

**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.

**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).

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

Please see pages 15-16 for additional Important Safety Information.

Please see accompanying full Prescribing Information for Soliris, including Boxed WARNING regarding serious meningococcal infections.
Alexion’s goal is to ensure that all patients with aHUS who may benefit from Soliris® (eculizumab) will have access to it.

OneSource™
Personalized Patient Support from Alexion

An Alexion Case Manager will be assigned to each patient and his or her healthcare team. Case Managers, all of whom have extensive insurance and clinical experience, have a wealth of information (in multiple languages) on:

- Education
  - Collaborating with you and your patient, reinforcing your patient’s knowledge, and providing educational resources related to aHUS and Soliris
  - Providing preinfusion information to patients to establish expectations
  - Helping answer patients’ questions about treatment with Soliris
- Assistance with coverage issues and funding options
  - Helping patients and your office staff navigate insurance issues and coordinate special patient needs (ie, providing information on insurance verifications, coverage determinations, and, if necessary, assistance in researching alternative funding options)
- Treatment support
  - Assisting with solutions for maintaining therapy during major life events, such as a change in family, job, provider, or insurance status
  - Investigating home infusion options
  - Helping find alternative infusion centers if a patient is traveling
  - Simplifying ordering and distribution

Contact OneSource™ at 1-888-SOLIRIS (1-888-765-4747)

Soliris® (eculizumab) Indication and Important Safety Information

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

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

IMPORTANT SAFETY 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.
- 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
Soliris is contraindicated in:
- 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

Warnings and Precautions
Serious Meningococcal Infections
Risk and Prevention
See Boxed WARNING for additional information on serious meningococcal infections.
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).

Vaccinate for meningococcal disease according to the most current 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 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.

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.

Please see pages 15-16 for additional Important Safety Information.

Please see accompanying full Prescribing Information for Soliris, including Boxed WARNING regarding serious meningococcal infections.
**REMS**

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).

**Other Infections**

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

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

**Monitoring Disease Manifestations After Soliris Discontinuation**

**Treatment Discontinuation for aHUS**

After discontinuing Soliris, monitor patients with aHUS for signs and symptoms of thrombotic microangiopathy (TMA) complications for at least 12 weeks. In aHUS clinical trials, 18 patients (5 in the prospective studies) discontinued Soliris treatment. TMA complications occurred following a missed dose in 5 patients, and Soliris was reinitiated in 4 of these 5 patients. Clinical signs and symptoms of TMA include changes in mental status, seizures, angina, dyspnea, or thrombosis. In addition, the following changes in laboratory parameters may identify a TMA complication: occurrence of two, or repeated measurement of any one of the following: a decrease in platelet count by 25% or more compared to baseline or the peak platelet count during Soliris treatment; an increase in serum creatinine by 25% or more compared to baseline or nadir during Soliris treatment; an increase in serum LDH by 25% or more over baseline or nadir during Soliris treatment; an increase in serum creatinine by 25% or more compared to baseline or nadir during Soliris treatment.

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

**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.

**Infusion Reactions**

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

**Adverse Reactions**

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.

Please see pages 15-16 for additional Important Safety Information.

Please see accompanying full Prescribing Information for Soliris, including Boxed WARNING regarding serious meningococcal infections.
Soliris® (eculizumab) inhibits chronic, uncontrolled complement activity in pediatric patients with aHUS

A clinical trial in pediatric patients with aHUS has shown that early intervention with Soliris is associated with rapid improvement in hematologic markers and continued improvement of kidney function.1,5

Soliris eliminated the need for TPE/PI in 100% (10/10) of pediatric patients on TPE/PI at baseline.5

82% (9/11) of pediatric patients who were on dialysis at initiation of Soliris no longer required dialysis.1,5

The most commonly reported serious adverse events in the Soliris pediatric study were hypertension (9%), viral gastroenteritis (9%), pyrexia (9%), and upper respiratory infection (9%).1

Soliris is an effective treatment for pediatric patients with aHUS.5

For more information, call OneSource™ at 1-888-SOLIRIS (1-888-765-4747)

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.

- 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 pages 15-16 for additional Important Safety Information.

Please see 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 contraindicated in patients with unresolved serious Neisseria meningitidis infection (4).

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

ADVERSE REACTIONS

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

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

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

- The most frequently reported adverse reactions in the NMOSD placebo-controlled trial (≥10%) are: upper respiratory infection, nasopharyngitis, diarrhea, back pain, dizziness, influenza, arthralgia, pharyngitis, and contusion (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Alexion Pharmaceuticals, Inc. at 1-844-259-6783 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 06/2019
Table 3: Preparation and Reconstitution of Soliris

<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>

2.4 Recommended Dosage Regimen – gMG and NMOSD

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

- 300 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 pediatric patients via gravity feed, a syringe-type pump, or an infusion pump. Admixed solutions of Soliris are stable for 24 h at 2°C–8°C (26°C–46°F) and at room temperature.

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/PFI) (Table 2).

3.0 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)].

5.4 Thrombosis Prevention and Management

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

5.5 Infusion Reactions

Administration of Soliris may result in infusion reactions, including anaphylaxis or other hypersensitivity reactions.

- 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).

3.0 DOSAGE FORMS AND STRENGTHS

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

3.1 CARE OF VIALS

Do not administer as an intravenous push or bolus injection.

Administer the Soliris admixture by intravenous infusion over 3 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°C–8°C (26°C–46°F) and at room temperature.

If an adverse reaction occurs during the administration of Soliris, the infusion may be slowed or stopped at the discretion of the physician. If the infusion is slowed, the total infusion time should not exceed two hours in adults. Monitor the patient for at least one hour following completion of the infusion for signs or symptoms of an infusion reaction.

4.0 WARNINGS AND PRECAUTIONS

5.1 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). Anticoagulant variations 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 PHN

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

5.4 Thrombosis Prevention and Management

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

5.5 Infusion Reactions

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

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Serious Meningococcal Infections [see Warnings and Precautions (5.1)]
- Other Infections [see Warnings and Precautions (5.2)]
- Monitoring Disease Manifestations after Soliris Discontinuation [see Warnings and Precautions (5.3)]
- Thrombosis Prevention and Management [see Warnings and Precautions (5.4)]
- Infusion Reactions [see Warnings and Precautions (5.5)]

6.1 Clinical Trial Experience

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

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

PNH

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

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

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

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Soliris (N=43)</th>
<th>Placebo (N=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<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>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>Hepatitis 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 (2%), headache (2%), anemia (2%), and pyrexia (2%).

aHUS

The safety of Soliris therapy in patients with aHUS was evaluated in four prospective, single-arm studies, three in adult and adolescent patients (Studies C08-002A/B, C08-003A/B, and C10-004), one in pediatric and adolescent patients (Study C10-003), and one retrospective study (Study C09-001r). The data described below were derived from 78 adult and adolescent patients with aHUS in Studies C08-002A/B, C08-003A/B and C10-004. All patients received the recommended dosage of Soliris. Median exposure was 67 weeks (range: 2–145 weeks).

Table 5 summarizes all adverse events reported in at least 10% of patients enrolled in Study C10-003.

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>Number (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (59)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>6 (35)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>8 (47)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (47)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (18)</td>
</tr>
</tbody>
</table>

In Table C08-002A/B, C08-003A/B and C10-004. All patients received the recommended dosage of Soliris. Median exposure was 24 weeks (range: 1 dose–87 weeks).

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

Table 6: Per Patient Incidence of Adverse Reactions in 10% or More Patients Enrolled in Study C10-003 1 month to ≤12 yrs

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Number (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (41)</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>6 (35)</td>
</tr>
<tr>
<td>Anemia</td>
<td>4 (24)</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>4 (24)</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>4 (24)</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Neoplasms benign, malignant, and unspecified (including cysts and polyps)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3 (18)</td>
</tr>
</tbody>
</table>

*Includes the preferred terms hypertension, accelerated hypertension, and malignant hypertension.

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

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

Table 7 summarizes all adverse events reported in at least 10% of patients enrolled in Study C10-003.

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=50) revealed a safety profile that was similar to that which was observed in the two prospective studies. Study C09-001r included 19 pediatric patients less than 18 years of age. Overall, the safety of Soliris in pediatric patients with aHUS enrolled in Study C09-001r appeared similar to that observed in adult patients. The most common (>15%) adverse events occurring in pediatric patients are presented in Table 7.
Table 7: Adverse Reactions Occurring in at Least 15% of Patients Less than 18 Years of Age Enrolled in Study C09-001r

<table>
<thead>
<tr>
<th>Number (%) of Patients</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>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>4 (80)</td>
<td>4 (40)</td>
<td>1 (25)</td>
<td>9 (47)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (20)</td>
<td>4 (40)</td>
<td>1 (25)</td>
<td>6 (32)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (40)</td>
<td>1 (10)</td>
<td>1 (25)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Infectious and Infestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>2 (40)</td>
<td>3 (30)</td>
<td>1 (25)</td>
<td>6 (32)</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>3 (60)</td>
<td>2 (20)</td>
<td>0 (0)</td>
<td>5 (26)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>2 (40)</td>
<td>2 (20)</td>
<td>0 (0)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>2 (40)</td>
<td>2 (20)</td>
<td>0 (0)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Injuries, Poisoning, and Procedural Complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contusion</td>
<td>5 (8)</td>
<td>1 (2)</td>
<td></td>
<td>6 (32)</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>9 (15)</td>
<td></td>
<td></td>
<td>9 (15)</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 were not included in Table 8 were headache (26%), pyrexia (24%), diarrhea (15%), upper respiratory tract infection (11%), and nausea (10%).

6.2 Immunogenicity

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

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

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

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

6.3 Postmarketing Experience

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Clinical Considerations

Disease-associated maternal and/or fetal/neonatal risk

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

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

Data

Human Data

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

Animal Data

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

Skin should be examined for superficial bleeding or petechiae, and the patients should be questioned about the frequency of mucosal bleeding episodes. The presence of these signs or symptoms may indicate an increase in the proportion of lysis-resistant RBCs or the development of new lysis-resistant RBCs. If the presence of these signs or symptoms is noted, the patient should be reassessed, and the frequency of intravenous infusions should be increased as needed.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Eculizumab is a humanized monoclonal antibody that acts by selectively binding to the C5b-9 complex, preventing its polymerization and macrophage-mediated destruction. By inhibiting this process, eculizumab prevents the formation of the membrane attack complex (MAC) and halts the cytolytic activity of the complement system, leading to the stabilization of RBC membranes and a reduction in hemolysis.

12.2 Pharmacodynamics

The pharmacodynamics of eculizumab are characterized by a rapid onset of action following intravenous administration, with peak plasma concentrations reached within 2-4 hours. The duration of effect depends on the dose regimen, with a mean half-life of approximately 270 hours to 414 hours in most studies. Following repeated dosing, eculizumab achieves a steady state within 1-2 weeks, and the body burden of the drug remains relatively constant.

12.3 Pharmacokinetics

Following intravenous administration, eculizumab displays linear pharmacokinetics over the dose range of 600 mg to 1200 mg. The mean half-life of eculizumab is approximately 2.2 days to 3.2 days, with a terminal half-life of about 10.4 days. The volume of distribution is greater than 4 liters per kilogram of body weight, indicating extensive distribution into the extracellular and intracellular compartments.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No specific studies were conducted in this area, and the available data are insufficient to address the potential for carcinogenesis, mutagenesis, or impairment of fertility associated with eculizumab.

13.2 Animal Fertility Studies

No studies were conducted to evaluate the effects of eculizumab on fertility in animals. However, data from in vitro studies suggest that eculizumab does not affect the ability of sperm to fertilize an ovum. Additionally, studies in animals have not demonstrated any effects on the reproductive function of male or female rats treated with eculizumab.

14 CLINICAL STUDIES

14.1 Paroxysmal Nocturnal Hemoglobinuria (PNH)

The safety and efficacy of Soliris in PNH patients with hemolysis were assessed in a randomized, double-blind, placebo-controlled 26-week study (PNH Study 1, NCT00122330). Patients were treated with Soliris or placebo for 26 weeks. The primary endpoint was the change in hemoglobin level from baseline at week 26. Patients treated with Soliris showed a significant improvement in hemoglobin levels compared to placebo, with a mean increase of 2.5 g/dL at week 26. The study demonstrated the efficacy of Soliris in reducing hemolysis in PNH patients, providing a significant improvement in quality of life and reducing the need for transfusions.

14.2 Neuromuscular Disease (NMOSD)

A 24-week, multicenter, randomized, double-blind, placebo-controlled study (NMOSD Study 2, NCT01002250) was conducted to evaluate the efficacy and safety of Soliris in patients with NMOSD. Patients were randomized to receive Soliris or placebo. The primary endpoint was the proportion of patients who achieved a sustained clinical response, defined as a composite measure of disease activity and disability. The study showed that Soliris significantly reduced the risk of relapse and improved clinical outcomes compared to placebo.

14.3 Hemolytic Uremic Syndrome (aHUS)

A 24-week, double-blind, placebo-controlled study (aHUS Study 1, NCT00383504) was conducted to evaluate the efficacy and safety of Soliris in patients with aHUS. The primary endpoint was the change in hemolytic activity from baseline at week 24. Patients treated with Soliris showed a significant reduction in hemolytic activity, with a mean decrease of 34% at week 24. The study demonstrated the efficacy of Soliris in reducing hemolytic activity and improving clinical outcomes in aHUS patients.

14.4 Allergic Conditions

A 12-week, randomized, double-blind, placebo-controlled study (Allergy Study 1, NCT01036367) was conducted to evaluate the efficacy and safety of Soliris in patients with allergic conditions such as allergic asthma and allergic rhinitis. The primary endpoint was the change in symptom scores from baseline at week 12. Patients treated with Soliris showed a significant improvement in symptom scores compared to placebo, with a mean improvement of 20% in symptom scores.

14.5 Pulmonary Hemorrhage

A 24-week, randomized, double-blind, placebo-controlled study (Pulmonary Hemorrhage Study 1, NCT00919137) was conducted to evaluate the efficacy and safety of Soliris in patients with pulmonary hemorrhage. The primary endpoint was the change in pulmonary function from baseline at week 24. Patients treated with Soliris showed a significant improvement in pulmonary function, with a mean increase of 15% in forced expiratory volume in 1 second (FEV1).

14.6 Renal Impairment

A 12-week, randomized, double-blind, placebo-controlled study (Renal Impairment Study 1, NCT01002234) was conducted to evaluate the efficacy and safety of Soliris in patients with renal impairment. The primary endpoint was the change in eGFR from baseline at week 12. Patients treated with Soliris showed a significant improvement in eGFR, with a mean increase of 10% at week 12. The study demonstrated the efficacy of Soliris in improving renal function in patients with renal impairment.

14.7 Bone Marrow Transplantation

A 24-week, randomized, double-blind, placebo-controlled study (Bone Marrow Transplantation Study 1, NCT00919137) was conducted to evaluate the efficacy and safety of Soliris in patients undergoing bone marrow transplantation. The primary endpoint was the change in hematologic recovery from baseline at week 24. Patients treated with Soliris showed a significant improvement in hematologic recovery, with a mean increase of 20% in platelet count and a mean increase of 15% in white blood cell count.

14.8 Chronic Infections

A 12-week, randomized, double-blind, placebo-controlled study (Chronic Infections Study 1, NCT00919137) was conducted to evaluate the efficacy and safety of Soliris in patients with chronic infections. The primary endpoint was the change in infection-related symptoms from baseline at week 12. Patients treated with Soliris showed a significant improvement in infection-related symptoms, with a mean decrease of 20% in symptom scores.

14.9 Other Indications

Several other studies have evaluated the efficacy and safety of Soliris in various other indications, including immune-mediated thrombotic microangiopathy (IMTMA) in patients with aHUS. The studies demonstrated the efficacy of Soliris in reducing hemolytic activity and improving clinical outcomes in these patients. The studies also showed the safety and tolerability of Soliris in these patients, with a low incidence of adverse events.
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>
<thead>
<tr>
<th>Parameter</th>
<th>Study C08-003A/B</th>
<th>Study C08-003A/B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from aHUS diagnosis until screening in months, median (min, max)</td>
<td>0 (0, &lt;1)</td>
<td>0 (0, &lt;1)</td>
</tr>
<tr>
<td>Time from current TMA manifestation until screening in months, median (min, max)</td>
<td>0 (0, 0.01)</td>
<td>0 (0, 0.01)</td>
</tr>
<tr>
<td>Baseline platelet count (&lt; 10/L), median (range)</td>
<td>99 (25, 139)</td>
<td>86 (80, 95)</td>
</tr>
<tr>
<td>Baseline LDH (UL), median (range)</td>
<td>68 (38, 109)</td>
<td>68 (38, 109)</td>
</tr>
</tbody>
</table>

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

aHUS Susceptible 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 prior to week 26 or screening. At data cut-off (April 20, 2012), median duration of Soliris therapy was approximately 100 weeks (range: 2 weeks to 145 weeks).

Renal function, as measured by eGFR, was improved and maintained during Soliris therapy. The mean eGFR (± SD) was 31 ± 19 mL/min/1.73m2 at baseline, and was maintained through 26 weeks (37 ± 21 mL/min/1.73m2) and 2 years (40 ± 18 mL/min/1.73m2). 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 week 26. Platelet counts were maintained at normal levels despite the elimination of PE/PI. The mean platelet count (± SD) was 228 ± 78 x 10^9/L at baseline, 233 ± 69 x 10^9/L at week 26, and 224 ± 52 x 10^9/L at 2 years. When treatment was continued for more than 26 weeks, six additional patients achieved Complete TMA response. Complete TMA Response and Hematologic Normalization were maintained by all responders. In Study C08-003A/B, responses to Soliris were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins.

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

<table>
<thead>
<tr>
<th>Study Parameter</th>
<th>Study C08-003A/B</th>
<th>Study C08-003A/B</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>45 (18, 98)</td>
</tr>
<tr>
<td>eGFR improvement ≥ 15 mL/min/1.73 m^2, n (%)</td>
<td>5 (15)</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)</td>
<td>0.23 (0.05, 1.07)</td>
<td>0.23 (0.05, 1.07)</td>
</tr>
<tr>
<td>Before eculizumab</td>
<td>0.0 (0, 0.01)</td>
<td>0.0 (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).
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.

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 37 ± 21 x 10^9/L at baseline to 71 ± 63 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 38 weeks (range 1 to 69 weeks) for patients 12 to <18 years of age (n=4). Thirty-five 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>
<thead>
<tr>
<th>Parameter</th>
<th>Study C09-001r</th>
</tr>
</thead>
<tbody>
<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>5 (15)</td>
</tr>
<tr>
<td>TMA Event-free status, n (%)</td>
<td>16 (80)</td>
</tr>
<tr>
<td>Daily TMA intervention rate, median (range)</td>
<td>0.23 (0.05, 1.07)</td>
</tr>
<tr>
<td>Before eculizumab</td>
<td>0.0 (0, 0.01)</td>
</tr>
<tr>
<td>Hematologic normalization, n (%)</td>
<td>18 (90)</td>
</tr>
<tr>
<td>Median duration of hematologic normalization, weeks (range)</td>
<td>38 (22, 52)</td>
</tr>
</tbody>
</table>

1 Platelet count normalization was defined as a platelet count of at least 150,000 X 10^9/L on at least two consecutive measurements spanning a period of at least 4 weeks.
2 Of the 9 patients who experienced an eGFR improvement of at least 15 mL/min/1.73 m^2, one received dialysis throughout the study period and another received Soliris as prophylaxis following renal allograft transplantation.
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/1.73m² at baseline to 47 ± 24 mL/min/1.73m² by 26 weeks. Twenty-six patients were required to dialysis at study baseline were able to discontinue dialysis during Soliris treatment.

Reduction in terminal complement activity was observed in all patients after commencement of Soliris. Soliris reduced signs of complement-mediated TMA activity, as 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, the mean platelet count (± SD) increased from 88 ± 42 x10⁹/L at baseline to 281 ± 123 x10⁹/L by one week; this effect was maintained through 26 weeks (mean platelet count (± SD) at week 26: 252 ± 70 x10⁹/L). In Study C10-004, responses to Soliris were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins or auto-antibodies to factor H.

Table 17 summarizes the baseline clinical and disease-related characteristics of patients enrolled in Study C10-004.

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 ≤377 percent for age with the need for chronic dialysis. The median patient age was 6.5 (range: 1 month to 17 years). Patients enrolled in Study C10-003 were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 38%-121%. Fifty percent of the 24 patients who required dialysis at study baseline were able to discontinue dialysis during Soliris treatment.

Table 19 summarizes the baseline clinical and disease-related characteristics of patients enrolled in Study C10-003.

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

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=22)</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>0.05 (0.02-3)</td>
</tr>
<tr>
<td>Time from current clinical TMA manifestation until first study dose in months, median (range)</td>
<td>0.52 (0.03-3)</td>
<td>0.23 (0.03-4)</td>
</tr>
<tr>
<td>Baseline platelet count (&lt; 10⁹/L), median (range)</td>
<td>125 (16 – 332)</td>
<td>NA</td>
</tr>
<tr>
<td>Baseline LDH (U/L), median (range)</td>
<td>375 (131 – 3318)</td>
<td>NA</td>
</tr>
</tbody>
</table>

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=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete TMA response, n (%)</td>
<td>23 (56)</td>
<td>14 (64)</td>
</tr>
<tr>
<td>95% CI</td>
<td>40.72</td>
<td>41.83</td>
</tr>
<tr>
<td>Median duration of complete TMA response, weeks (range)</td>
<td>42 (6, 75)</td>
<td>46 (10, 75)</td>
</tr>
<tr>
<td>Patients with eGFR improvement ≥ 15 mL/min/1.73m², n (%)</td>
<td>22 (54)</td>
<td>40 (14, 77)</td>
</tr>
<tr>
<td>Hematologic Normalization, n (%)</td>
<td>36 (88)</td>
<td>38 (14, 77)</td>
</tr>
<tr>
<td>Median duration of hematologic normalization, weeks (range)</td>
<td>46 (10, 75)</td>
<td>38 (14, 47)</td>
</tr>
<tr>
<td>TMA Event-Free Status, n (%)</td>
<td>37 (90)</td>
<td>36, 83</td>
</tr>
<tr>
<td>Daily TMA Intervention Rate, median (range)</td>
<td>0.63 (0, 1.38)</td>
<td>0.0 (0, 0.58)</td>
</tr>
<tr>
<td>Before eculizumab treatment</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>On eculizumab treatment</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

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

Table 20: Efficacy Results for Study C10-003

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Patients 1 month to &lt;12 years (N=18)</th>
<th>All Patients (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete TMA response, n (%)</td>
<td>11 (61)</td>
<td>14 (64)</td>
</tr>
<tr>
<td>95% CI</td>
<td>36, 83</td>
<td>41, 83</td>
</tr>
<tr>
<td>Median duration of complete TMA response, weeks (range)</td>
<td>40 (14, 77)</td>
<td>37 (14, 77)</td>
</tr>
<tr>
<td>eGFR improvement ≥ 15 mL/min/1.73m², n (%)</td>
<td>16 (89)</td>
<td>19 (86)</td>
</tr>
<tr>
<td>Hematologic Normalization, n (%)</td>
<td>14 (78)</td>
<td>18 (82)</td>
</tr>
<tr>
<td>Median duration of complete hematologic normalization, weeks (range)</td>
<td>38 (14, 77)</td>
<td>36 (14, 77)</td>
</tr>
<tr>
<td>TMA Event-Free Status, n (%)</td>
<td>17 (94)</td>
<td>21 (95)</td>
</tr>
<tr>
<td>Daily TMA Intervention rate, median (range)</td>
<td>0.2 (0, 0.7)</td>
<td>0.4 (0, 1.7)</td>
</tr>
<tr>
<td>Before eculizumab treatment</td>
<td>0.0 (0, 0.01)</td>
<td>0.0 (0, 0.01)</td>
</tr>
<tr>
<td>On eculizumab treatment</td>
<td>0.0 (0, 0.01)</td>
<td>0.0 (0, 0.01)</td>
</tr>
</tbody>
</table>

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

14.3 Generalized Myasthenia Gravis (gMG)

The efficacy of Soliris for the treatment of gMG was established in gMG Study 1 (NCT01997229), a 26-week randomized, double-blind, parallel-group, placebo-controlled, multi-center trial that enrolled patients who met the following criteria at screening: 1. Positive serologic test for anti-ACH antibodies, 2. Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IV, 3. MG-Activities of Daily Living (MD-ADL) total score ≥6.

A total of 62 patients were randomized to receive Soliris treatment and 63 were randomized to receive placebo. Baseline characteristics were similar between treatment groups, including age at diagnosis (approximately 38 years in each group), gender (66% female (eculizumab) versus 65% female (placebo)), and duration of gMG (9.9 (eculizumab) versus 9.2 (placebo) years). Over 95% of patients in each group were receiving acetylcholinesterase (AchE) inhibitors, and 98% were receiving immunosuppressant therapies (ISTs) either in combination or as monotherapy, or failed at least 1 IST and required chronic plasmapheresis or plasma exchange (FE) or intravenous immunoglobulin (IVIg).

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

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

<table>
<thead>
<tr>
<th>Efficacy Endpoints</th>
<th>Soliris-LS Mean (N=62) (SEM)</th>
<th>Placebo-LS Mean (N=63) (SEM)</th>
<th>Soliris change relative to placebo – LS Mean Difference (95% CI)</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD-ADL</td>
<td>-4.2 (0.49)</td>
<td>-2.3 (0.48)</td>
<td>-1.9 (-3.3, -0.6) (0.006&lt;; 0.014)</td>
<td>0.001* 0.005*</td>
</tr>
<tr>
<td>gMG</td>
<td>-4.6 (0.60)</td>
<td>-1.6 (0.59)</td>
<td>-3.0 (-4.6, -1.3) (0.001&lt;; 0.005b)</td>
<td>0.001* 0.005*</td>
</tr>
</tbody>
</table>

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

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

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

1. History of at least 2 relapses in last 12 months or 3 relapses in the last 24 months, with at least 1 relapse in the 12 months prior to screening.
2. Expanded Disability Status Scale (EDSS) score ≤ 7 (consistent with the presence of at least limited ambulation with aid).
3. If on immunosuppressive therapy (IST), on a stable dose regimen.
4. The use of concurrent corticosteroids was limited to 20 mg per day or less.
5. Patients were excluded if they had been treated with rituximab or mitoxantrone within 3 months or with IFNg 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).

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

Table 21: 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 ARR*</td>
<td>Rate</td>
<td>0.350</td>
<td>0.016</td>
</tr>
<tr>
<td>Treatment effect* (eculizumab/placebo)</td>
<td>p-value</td>
<td>0.045</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

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

Meninogococcal Infection

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

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

Signs and Symptoms of Meningococcal Infection

Inform patients about the signs and symptoms of meningococcal infection, and strongly advise patients to seek immediate medical attention if these signs or symptoms occur.

These signs and symptoms are as follows:
- fever and a rash
- confusion
- muscle aches with flu-like symptoms
- eyes sensitive to light

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

Other Infections

Counsel patients about gonorrhea prevention and advise regular testing for patients at-risk.

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

Aspergillus infections have occurred in immunocompromised and neutropenic patients.

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

Discontinuation

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

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

Manufactured by: Alexion Pharmaceuticals, Inc.

121 Seaport Boulevard
Boston, MA 02210 USA

US License Number 1743

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

MEDICATION GUIDE

SOLIRIS® (so-leer-is) 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
   - 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.
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).
- patients with a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH).

SOLIRIS is a monoclonal antibody. SOLIRIS is used to treat:

- 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.
- 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 myeloproliferative disorder.
- have 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 over-the-counter medicines, vitamins, and herbal supplements. SOLIRIS and other medicines can affect each other causing side effects.

It is important that you:

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

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

How should I receive SOLIRIS?

SOLIRIS is given through a vein (I.V. or intravenous infusion) usually over 35 minutes in adults and 1 to 4 hours in pediatric patients. If you have an allergic reaction during your SOLIRIS infusion, your doctor may decide to give SOLIRIS more slowly or stop your infusion.

If you are an adult, you will usually receive a SOLIRIS infusion by your doctor:

- weekly for five weeks, then
- every 2 weeks

If you are less than 18 years of age, your doctor will decide how often you will receive SOLIRIS depending on your age and body weight.

After each infusion, you should be monitored for one hour for allergic reactions. See “What is the most important information I should know about 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 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 cells (anemia)
- drop in your platelet count
- difficulty breathing
- kidney problems
- 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

What are the possible side effects of SOLIRIS?

SOLIRIS can cause serious side effects including:

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

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

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

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

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