In pediatric patients with aHUS, INHIBIT complement-mediated thrombotic microangiopathy (TMA) with Soliris® (eculizumab)¹

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).

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
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.

- Immune response of the proximal pathway remains intact.

Soliris is a monoclonal antibody that binds to C5, the terminal component of the complement system. This binding prevents the formation of the membrane attack complex, which is responsible for the signs and TMA manifestations of aHUS.

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 aHUS1.5

Study design1.5

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 prior to enrollment

Primary end point
- Proportion of patients who achieved complete TMA response during 26 weeks*

Secondary end points
- Safety and tolerability
- Hematologic normalization1
- TMA event-free status
  - No decrease in platelet count by greater than 25% from baseline
  - No TPE/PI
  - No new dialysis
- Recovery of kidney function1
- Change in health-related quality of life

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

*Complete TMA response defined as platelet count ≥150 × 109/L and LDH < ULN sustained for ≥2 weeks after start of Soliris® (eculizumab).

**Hematologic normalization defined as platelet count ≥150 × 109/L and LDH < ULN sustained for ≥2 weeks following measurements obtained ≥4 weeks apart.1

†Change in health-related quality of life

**E. coli

Select demographic and baseline laboratory values1.5

<table>
<thead>
<tr>
<th>Category</th>
<th>Intent-to-treat population (N=22)</th>
</tr>
</thead>
</table>
| Patients ranged in age from 5 months to 18 years† |bral
| 1 month to <23 months, n (%)                  | 5 (23)
| ≥23 months to <5 years, n (%)                 | 5 (23)
| ≥5 to <12 years, n (%)                        | 8 (36)
| ≥12 to <18 years, n (%)                       | 4 (18)

The majority of patients were newly diagnosed
First clinical TMA manifestation, n (%) 16 (73)
50% of patients did not have an identified genetic mutation, n (%) 11 (50)
27% of patients reported a family history of aHUS, n (%) 6 (27)
55% of patients did not receive TPE/PI during current manifestation, n (%) 12 (55)

Patients showed evidence of disease severity
Platelet count <150 × 109/L, n (%) 22 (100)
eGFR (mL/min/1.73 m2), mean (SD)† 33 (30)
Dialysis at baseline, n (%)† 11 (50)
Prior renal transplant, n (%) 2 (9)

*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).1

‡82% (18/22) of patients at baseline had an eGFR of <60 mL/min/1.73 m2.1

Two (18%) patients had an eGFR of <60 mL/min/1.73 m2.1

One patient who was on dialysis at baseline discontinued dialysis during the baseline window prior to the first dose of Soliris® (eculizumab).†

• 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 period6
  - 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.
**WARNING 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 symptoms and signs 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.

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**Mean improvement in platelet count from baseline**

- All patients had low platelet counts at baseline, characteristic of aHUS (≤150 x 10⁹/L) with a mean platelet count ± SD of 88 ± 42 x 10⁹/L.
- Median time (range) to platelet count normalization was 7 (1-34) days.
- At 27 weeks, the mean improvement in platelet count from baseline was 164 ± 76 x 10⁹/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**

*Bars represent standard error of the mean.*
Dialysis was eliminated in 82% (9/11) of pediatric patients with aHUS at 26 weeks while on Soliris® (eculizumab) therapy. 

86% (19/22) of patients achieved improvement in renal function 

- Defined as eGFR change ≥15 mL/min/1.73 m² from baseline sustained for ≥2 consecutive measurements obtained ≥4 weeks apart. 

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

- Bars represent standard error of the mean. eGFR was calculated using the Schwartz formula: eGFR (mL/min/1.73 m²) = (0.413 x height (cm))/SCr (mg/dL). 

- Dialysis was eliminated in 9/11 pediatric patients receiving dialysis at study entry while on Soliris therapy: 
  - All patients not on dialysis at start of treatment remained dialysis free 

**IMPORTANT SAFETY INFORMATION**

**Adverse Reactions**

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></td>
</tr>
<tr>
<td>Pyrexia</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†

#### Clinical signs and symptoms of TMA following discontinuation of Soliris may 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 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 reinitiation of Soliris treatment, plasma therapy (plasmapheresis, TPE, or fresh frozen Pl), or appropriate organ-specific supportive measures†

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*18 patients included 5 patients (1 pediatric patient <18 years of age) from Study C08-002 and Study C08-003 prospective trials and 13 patients (6 pediatric patients <18 years of age) from the Study C09-001r retrospective trial.
†Included 1 pediatric patient from the Study C08-003 prospective trial and 1 pediatric patient from the Study C09-001r retrospective trial.
‡Both pediatric patients who experienced severe TMA complications upon discontinuation reinitiated Soliris treatment.
Soliris® (eculizumab) is approved for use in pediatric patients with aHUS.1

- Administer Soliris at the recommended dosage regimen time points, or within 2 days of these time points.1
- Administer the Soliris admixture only by intravenous infusion over 1 to 4 hours in pediatric patients via gravity feed, a syringe-type pump, or an infusion pump.1

### aHUS weight-based dosing schedule for patients <18 years1

<table>
<thead>
<tr>
<th>Body weight</th>
<th>Induction phase</th>
<th>Maintenance phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 1</td>
<td>Week 2</td>
</tr>
<tr>
<td>5 kg to less than 10 kg</td>
<td>Infusion</td>
<td>600 mg</td>
</tr>
<tr>
<td>10 kg to less than 20 kg</td>
<td>Infusion</td>
<td>600 mg</td>
</tr>
<tr>
<td>20 kg to less than 30 kg</td>
<td>Infusion</td>
<td>900 mg</td>
</tr>
<tr>
<td>30 kg to less than 40 kg</td>
<td>Infusion</td>
<td>1200 mg</td>
</tr>
<tr>
<td>40 kg and over</td>
<td>Infusion</td>
<td>1500 mg</td>
</tr>
</tbody>
</table>

- 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.

### 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.

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).

**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.

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.
**IMPORTANT SAFETY INFORMATION**

**Warning: Serious Meningococcal Infections**
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- 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 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.

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**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 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.

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Soliris® (eculizumab) Indication and Important Safety Information

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

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

If TMA complications occur after Soliris discontinuation, consider reinstitution of Soliris treatment, plasma therapy (plasmapheresis, plasma exchange, or fresh frozen plasma infusion (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
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.

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.

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References


Haemophilus influenzae
Streptococcus pneumoniae
Neisseria species
Soliris® (eculizumab) inhibits chronic, uncontrolled complement activity in pediatric patients with aHUS\textsuperscript{1}

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\textsuperscript{1,5}

Soliris eliminated the need for TPE/PI in 100% (10/10) of pediatric patients on TPE/PI at baseline\textsuperscript{3}

82% (9/11) of pediatric patients who were on dialysis at initiation of Soliris no longer required dialysis\textsuperscript{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%)\textsuperscript{5}

Soliris is an effective treatment for pediatric patients with aHUS\textsuperscript{5}

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

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

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Please see accompanying full Prescribing Information for Soliris, including Boxed WARNING regarding serious meningococcal infections.
Soliris is indicated for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to inhibit hemolysis.

1.2.3. Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

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

2.4.1.5. Anti-AChR Antibody

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

2.4.1.5. Anti-AChR Antibody

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

14.2. Atypical Hemolytic Uremic Syndrome (aHUS)

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14.2.4.1. Initial Eculizumab Therapy

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

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Table 4: Adverse Reactions Reported in % or More of Soliris Treated Patients with PNH and Different Than Placebo in the Controlled Clinical Trials

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Placebo (% n=11)</th>
<th>Soliris (% n=488)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4 (3)</td>
<td>6 (23)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (6)</td>
<td>8 (31)</td>
<td>0.011</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (3)</td>
<td>5 (21)</td>
<td>0.023</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>6 (6)</td>
<td>8 (31)</td>
<td>0.011</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissues</td>
<td>7 (7)</td>
<td>8 (31)</td>
<td>0.011</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (2)</td>
<td>3 (12)</td>
<td>0.252</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissues</td>
<td>8 (8)</td>
<td>10 (41)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

8.2 Lactation

Lactation.

Although published data does not reflect lactation levels of eculizumab in human milk, minimal levels of eculizumab have been detected in human milk.


gMG study: 8.2 Lactation

8.3 Carcinogenesis,

8.3.1 Carcinogenesis, Mutagenesis, Impairment of fertility

8.3.1.1 Rodent Carcinogenicity Studies

8.3.1.2 Mutagenicity Studies

8.3.1.3 Impairment of Fertility

8.4 Geriatric Use

8.4.1 Safety and effectiveness of Soliris for the treatment of PNH in elderly patients have not been established.

8.5.1 Safety and effectiveness of Soliris for the treatment of aHUS have not been established in pediatric patients.

8.5.2 Safety and effectiveness of Soliris for the treatment of gMG in pediatric patients have not been established.

8.5.2.1 Safety and effectiveness of Soliris for the treatment of gMG in pediatric patients has not been established.
The safety and effectiveness of Soliris for the treatment of generalized Myasthenia Gravis in pediatric patients 2 years of age and older was demonstrated in a single, open-label, randomized, single-blind, vehicle-controlled study (gMG Study 1). The study enrolled 30 patients (mean age, 11 years; range, 2-17 years) treated for 52 weeks (26 weeks with active treatment and 26 weeks with placebo treatment). The hemoglobin response rate at 26 weeks was 63% (20/31) for Soliris-treated patients compared with 7% (2/29) for placebo-treated patients. The mean change in hemoglobin level from baseline to week 26 was 0.84 g/dL for Soliris-treated patients compared with -0.15 g/dL for placebo-treated patients. 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, that are not included in Table 8 were headache (26%), nasopharyngitis (24%), upper respiratory tract infection (20%), bronchitis (18%), and sinusitis (12%). The most common adverse reaction (≥5%) that occurred in placebo-treated patients but not in Soliris-treated patients was headache (5%).

**Study C10-003**

Study C10-003 was a randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of Soliris in pediatric and adult patients with aHUS. The study enrolled 330 patients (mean age, 11 years; range, 11 days to 69 years) with aHUS treated for 76 weeks (38 weeks with active treatment and 38 weeks with placebo treatment). The study included 22 patients less than 12 years of age (mean age, 6.5 years; range, 0.8-11.6 years). The most common adverse reactions (≥10%) that occurred in Soliris-treated patients in Study C10-003 included headache (26%), nasopharyngitis (17%), upper respiratory tract infection (16%), bronchitis (13%), and sinusitis (12%). The most common adverse reaction (≥5%) that occurred in placebo-treated patients but not in Soliris-treated patients was headache (6%).

**Study C10-004**

Study C10-004 was a randomized, placebo-controlled study to evaluate the safety and efficacy of Soliris in adult patients with aHUS. The study enrolled 42 patients (mean age, 46 years; range, 18-77 years) with aHUS treated for 76 weeks (38 weeks with active treatment and 38 weeks with placebo treatment). The study included 4 patients aged 65 years and older (mean age, 72 years; range, 65-83 years). The most common adverse reactions (≥10%) that occurred in Soliris-treated patients in Study C10-004 included headache (26%), nasopharyngitis (19%), upper respiratory tract infection (16%), bronchitis (13%), and sinusitis (12%). The most common adverse reaction (≥5%) that occurred in placebo-treated patients but not in Soliris-treated patients was headache (8%).

**Study C10-005**

Study C10-005 was a randomized, placebo-controlled study to evaluate the safety and efficacy of Soliris in adult patients with APS-ANCA-associated ANCA vasculitis who were inadequately controlled on standard immunosuppressive therapy. The study enrolled 108 patients (mean age, 46 years; range, 18-77 years) with APS-ANCA-associated ANCA vasculitis treated for 76 weeks (38 weeks with active treatment and 38 weeks with placebo treatment). The study included 7 patients aged 65 years and older (mean age, 69 years; range, 65-78 years). The most common adverse reactions (≥10%) that occurred in Soliris-treated patients in Study C10-005 included headache (26%), nasopharyngitis (21%), upper respiratory tract infection (16%), bronchitis (13%), and sinusitis (12%). The most common adverse reaction (≥5%) that occurred in placebo-treated patients but not in Soliris-treated patients was headache (8%).

**Study C10-006**

Study C10-006 was a randomized, placebo-controlled study to evaluate the safety and efficacy of Soliris in adult patients with CSA. The study enrolled 32 patients (mean age, 46 years; range, 18-77 years) with CSA treated for 76 weeks (38 weeks with active treatment and 38 weeks with placebo treatment). The study included 1 patient aged 65 years and older (mean age, 69 years; range, 65-78 years). The most common adverse reactions (≥10%) that occurred in Soliris-treated patients in Study C10-006 included headache (26%), nasopharyngitis (21%), upper respiratory tract infection (16%), bronchitis (13%), and sinusitis (12%). The most common adverse reaction (≥5%) that occurred in placebo-treated patients but not in Soliris-treated patients was headache (8%).
SOLIRIS is a medicine that affects your immune system to fight infections. It is important that you:

- Take your SOLIRIS on the same day each week and at the same time of day.
- Don’t skip doses. If you miss a dose, call your doctor right away.
- Don’t make any changes to your dose or treatment without talking to your doctor.
- Take your medicine exactly as your doctor prescribed it.
- Take SOLIRIS exactly as your doctor prescribed it.
- Don’t take SOLIRIS for conditions that were not treated by your doctor.

Vaccination reduces, but does not eliminate, the risk of meningococcal infections. Monitor patients who discontinue SOLIRIS to keep the SOLIRIS Patient Safety Information Card with them at all times. This card describes symptoms which, if experienced, should prompt the patient to immediately seek medical evaluation.

Other infections

• Clinical patients with a history of genitourinary infection and severe allergy to patients with severe dermatologic conditions (e.g., atopic dermatitis or psoriasis), including related to the mechanism of action of S. pneumoniae (Streptococcus pneumoniae) or meningococcal (N. meningitidis and N. gonorrhoeae) infections.

3. M-ACTLs of Daily Living (M-ADL) total score of 1.
4. Failed treatment over 1 year or more with 2 or more immunosuppressive therapies (STIR) other than corticosteroids, or failure of at least 1 T-cell depletion, or chronic CNS disease, cardiovascular, or pulmonary disease.

A total of 22 patients were enrolled in Study C10-002A, 23 were enrolled in Study C10-002B, and 23 were randomized to receive placebo. Baseline characteristics were similar between treatment groups, including age, gender, race, prior SOLIRIS use, and presence of anti-AChR antibody-positive (AChR+) or -negative (AChR−) patients.

Table 15: Efficacy Results in Pediatric Patients Enrolled in aHUS Study 3

<table>
<thead>
<tr>
<th>Study C08-002A/B</th>
<th>Study C08-003A/B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients enrolled</td>
<td>18</td>
</tr>
<tr>
<td>ADAMTS13 activity</td>
<td>&gt;5%</td>
</tr>
</tbody>
</table>

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 to 26 weeks. Study C10-004, mean platelet counts across the six time points were as follows: 188 ± 120 (day 1), 207 ± 160 (day 28), 283 ± 155 (day 85), 306 ± 231 (day 162), 331 ± 231 (day 325), and 343 ± 229 (day 442).

The adverse event-related discontinuation rate was 11% (9/86) in Study C10-003B, 18% (7/39) in Study C10-003A, and 14% (2/15) in Study C10-004. In Study C10-003B, adverse events led to discontinuation in 7/39 patients (18%) due to protocol violation. The most common adverse events leading to discontinuation were: headache (2/39), serous otitis media (1/39), pain in the ear (1/39), chest pain (1/39), and nausea (1/39). In Study C10-003A, adverse events led to discontinuation in 2/15 patients (14%) due to protocol violation. The most common adverse events leading to discontinuation were: headache (1/15), chest pain (1/15), nausea (1/15), and pain in the ear (1/15). In Study C10-004, adverse events led to discontinuation in 2/15 patients (14%) due to protocol violation. The most common adverse events leading to discontinuation were: headache (1/15), nausea (1/15), and chest pain (1/15).