**INDICATION**

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

**SELECT IMPORTANT SAFETY INFORMATION**

**WARNING: SERIOUS MENINGOCOCCAL INFECTIONS**

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

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.
- Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of Soliris, unless the risks of delaying Soliris therapy outweigh the risk of developing a meningococcal infection. (See Serious Meningococcal Infections for additional guidance on the management of the risk of meningococcal infection).
- Vaccination reduces, but does not eliminate, the risk of meningococcal infections. Monitor patients for early signs of meningococcal infections and evaluate immediately if infection is suspected.

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

Please see additional Important Safety Information throughout and accompanying full Prescribing Information for SOLIRIS, including Boxed WARNING regarding serious meningococcal infections.
Complement-mediated destruction of the NMJ occurs in many patients who have anti-AChR antibody-positive gMG.

Soliris® (eculizumab) is the first terminal complement inhibitor approved by the FDA to treat adult patients with anti-AChR antibody-positive gMG.

Abbreviations: NMJ, neuromuscular junction; TCC, terminal complement complex.

SELECT IMPORTANT SAFETY INFORMATION

Contraindications

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

Please see additional Important Safety Information throughout and accompanying full Prescribing Information for SOLIRIS, including Boxed WARNING regarding serious meningococcal infections.
Soliris® (eculizumab) was evaluated in REGAIN* in which the majority of patients were categorized as MGFA Classification mild (class II) to moderate (class III).2,4,5

### HISTORY OF TRIAL PARTICIPANTS

- 98% of patients received ≥2 ISTs at REGAIN baseline
- 46% received only 2 ISTs—including corticosteroids—at REGAIN baseline
- 28% received chronic IVIg, and 11% had received chronic PLEX
- Mean disease duration was 9.6 years
- 78% had a history of MG exacerbations
- 18% had a history of MG crisis

### HISTORICAL TRIAL PARTICIPANTS

- 91% of patients enrolled in the study had mild (38%) to moderate (53%) anti-AChR antibody-positive gMG at screening.

### SELECT IMPORTANT SAFETY INFORMATION

**Warnings and Precautions**

**Serious Meningococcal Infections**

**Risk and Prevention**

The use of Soliris increases a patient’s susceptibility to serious meningococcal infections (septicemia and/or meningitis). Vaccinate or revaccinate for meningococcal disease according to the most current ACIP recommendations for patients with complement deficiencies.

### SELECT IMPORTANT SAFETY INFORMATION

**Risk and Prevention (continued)**

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

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

Endpoints and baseline scores were measured using validated MG assessment tools.

### PRIMARY ENDPOINT

Change in MG-ADL total score from baseline to week 26 for eculizumab compared to placebo.

### SECONDARY ENDPOINT

Change in QMG total score from baseline to week 26 for eculizumab compared to placebo.

### MEASUREMENTS:

- Ocular, facial, bulbar, respiratory, and limb symptoms and their impact on functional activity
- Ocular, bulbar, respiratory, and limb symptoms and their impact on functional activity

### PATIENT-REPORTED

- Mean baseline score for patients in REGAIN (SD)

### PHYSICIAN-REPORTED

- Mean baseline score for patients in REGAIN (SD)

### Mean baseline scores were determined and compared to mean final scores at 26 weeks.2

### Abbreviations:

- ISTs, immunosuppressive therapies; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; PLEX, plasma exchange.
REGAIN and the open-label extension studies evaluated the efficacy and/or safety of Soliris® (eculizumab)²,⁵

STUDY DESIGN³

BREAKDOWN

SCREENING
SOC meningococcal vaccination

RANDOMIZATION

Soliris (n=62)
900 mg weekly x 4 then 1200 mg 1 week later (induction) then 1200 mg every 2 weeks (maintenance)

Placebo (n=63)

REGAIN (safety and efficacy)

26 WEEKS

Blinded Induction Phase⁴

Soliris/Soliris (n=56)
1200 mg every 2 weeks

Placebo/Soliris (n=61)
1200 mg every 2 weeks

Open-Label Study⁴ (safety)

208 WEEKS (4 YEARS)

SAFETY FOLLOW-UP AT 8 WEEKS⁴

After 26 weeks, patients who completed REGAIN were eligible to enter the open-label extension study.¹

Abbreviation: SOC, standard of care.

¹Interim data are reported from the December 31, 2017, data cutoff.

²During the blinded induction phase of the open-label study, patients received Soliris (1200 mg) at day 1 and week 2 and placebo at weeks 1 and 3 (Soliris/Soliris group), or placebo plus Soliris (900 mg) each week (placebo/Soliris group).

³Patients who withdrew or discontinued after receiving any amount of Soliris were required to complete a safety follow-up visit 8 weeks after their last Soliris dose.

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SELECT IMPORTANT SAFETY INFORMATION

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

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

(continued on page 9)

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

(continued on page 9)
Rapid and sustained improvement in activities of daily living (MG-ADL) through 26 weeks in REGAIN and observed up to 130 weeks during the open-label extension study.

**PRIMARY ENDPOINT** | Change in MG-ADL total score from baseline to week 26 for eculizumab compared to placebo

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Soliris (n=62)</th>
<th>Placebo (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥8</td>
<td>21%</td>
<td>6%</td>
</tr>
<tr>
<td>60%*</td>
<td>60%</td>
<td>40%</td>
</tr>
<tr>
<td>40%</td>
<td>40%</td>
<td>20%</td>
</tr>
<tr>
<td>20%</td>
<td>20%</td>
<td>0%</td>
</tr>
</tbody>
</table>

* Patients receiving Soliris showed improvement in MG-ADL in as early as 4 weeks after treatment initiation. This improvement was found to be sustainable for the duration of the 26-week study. Available data suggest that clinical response is usually achieved by 12 weeks of Soliris treatment.

**REGAIN Study Limitation**

Time to response was a tertiary endpoint and considered exploratory; therefore, results should be interpreted with caution.

**REGAIN OLE Study Limitation**

Observations in the open-label extension (OLE) study are based on an interim analysis with a primary goal of evaluating safety. Any inference of efficacy or clinical significance should be interpreted with caution since the study was open-label and lacked a control group.

**A majority of patients reported a clinically meaningful improvement in activities of daily living (MG-ADL) in REGAIN**

* Patients receiving Soliris showed improvement in MG-ADL in as early as 4 weeks after treatment initiation. This improvement was found to be sustainable for the duration of the 26-week study. Available data suggest that clinical response is usually achieved by 12 weeks of Soliris treatment.

† Testing the null hypothesis that there is no difference between the 2 treatment arms in least square means at week 26 using a repeated measure analysis.

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Improvements in muscle weakness (QMG) demonstrated in REGAIN were observed through week 130 of the open-label extension study interim analysis.2,5

SECONDARY ENDPOINT | Change in QMG total score from baseline to week 26 for eculizumab compared to placebo2

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Soliris/Soliris 52 52 52 48 48 48 46 23 13</th>
<th>Placebo/Soliris 60 57 57 55 53 53 48 24 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥10</td>
<td>16% 2%</td>
<td>45%*</td>
</tr>
<tr>
<td>≥9</td>
<td>45%*</td>
<td>39% 14%</td>
</tr>
<tr>
<td>≥8</td>
<td>34% 11%</td>
<td>27% 5%</td>
</tr>
<tr>
<td>≥7</td>
<td>23% 5%</td>
<td>23% 5%</td>
</tr>
<tr>
<td>≥6</td>
<td>19%</td>
<td>19%</td>
</tr>
<tr>
<td>≥5</td>
<td>40%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Mean total score at REGAIN baseline (IE) out of 39

Regain: n=62 (Soliris) = 63 (placebo)

Mean change in QMG total score from REGAIN baseline2,5

Soliris treatment effect was also evaluated in MG signs and symptoms and quality of life at week 26 in the REGAIN study.1

*Testing the null hypothesis that there is no difference between the 2 treatment arms in least square means at week 26 using a repeated measure analysis.1 Republished with permission of Muscle & Nerve. Permission conveyed through Copyright Clearance Center, Inc.

Regain OLE Study Limitation
Observations in the open-label extension (OLE) study are based on an interim analysis with a primary goal of evaluating safety. Any inference of efficacy or clinical significance should be interpreted with caution since the study was open-label and lacked a control group.

Regain OLE Select Safety Observations
Adverse events in the open-label extension study were consistent with REGAIN for up to 3 years. Infections were the most commonly reported adverse events of special interest. The most common serious AE was MG worsening (12.8%). There was 1 nonfatal case of meningococcal infection that was reported after data cutoff and was resolved with treatment. Three deaths occurred by the time of interim analysis. Cause of death was attributed to chronic hepatic failure, pulmonary embolism, and multi-organ failure (hepatic failure as primary).

*Based on a prespecified analysis of patients with a ≥5-point reduction in QMG total score (clinical responder) and who received no rescue therapy during REGAIN at 26 weeks.1

“QMG total scores at baseline were as follows: Soliris, median (min, max): ≥5 and ≥6, 17.5 (11, 31); ≥7, ≥8, and ≥9, 18.0 (12, 32); ≥10, 18.5 (3, 33); Placebo, median (min, max): ≥5, 20.5 (10, 29); ≥6, 22.0 (12, 29); ≥7, 23.0 (12, 29); ≥8, 25.0 (22, 29); ≥9, 22.0 (22, 22).” Republished with permission of Muscle & Nerve. Permission conveyed through Copyright Clearance Center, Inc.

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

Please see additional Important Safety Information throughout and accompanying full prescribing Information for SOLIRIS, including Boxed WARNING regarding serious meningococcal infections.
Clinical improvement was reported by the investigator prior to the interim analysis in the open-label extension study.

Minimal manifestations
The patient has no symptoms of functional limitations from MG but has some weakness on examination of some muscles. This class recognizes that some patients who otherwise meet the definition of pharmacologic remission do have weakness that is only detectable by careful examination.

Pharmacologic remission
While continuing to take some form of therapy for MG, the patient has had no symptoms or signs of MG for at least 1 year, and there is no weakness of any muscle on careful examination.

REGAIN OLE SELECT SAFETY OBSERVATIONS
Adverse events in the open-label extension study were consistent with REGAIN for up to 3 years. Infections were the most commonly reported adverse events of special interest. The most common serious AE was MG worsening (12.8%). There was 1 nonfatal case of meningococcal infection that was reported after data cutoff and was resolved with treatment. Three deaths occurred by the time of interim analysis. Cause of death was attributed to chronic hepatic failure, pulmonary embolism, and multi-organ failure (hepatic failure as primary).

EXACERBATION, HOSPITALIZATION, AND RESCUE THERAPY RATES OBSERVED IN AN INTERIM ANALYSIS OF THE OPEN-LABEL EXTENSION STUDY

75% REDUCTION IN EXACERBATION RATES
from prestudy baseline to week 130
Prestudy, 102.4 exacerbations per 100 patient-years; open-label study, 25.4 exacerbations per 100 patient-years

83% REDUCTION IN RATE OF MG-RELATED HOSPITALIZATIONS
from prestudy baseline to week 130
Prestudy, 81.3 hospitalizations per 100 patient-years; open-label study, 13.7 hospitalizations per 100 patient-years

66% REDUCTION IN RATE OF RESCUE THERAPY USE
for patients in the open-label extension study compared to REGAIN placebo group
23.1 events per 100 patient-years in the open-label study vs 67.5 events per 100 patient-years in patients receiving placebo during REGAIN

REGAIN OLE Study Limitation
Observations in the open-label extension (OLE) study are based on an interim analysis with a primary goal of evaluating safety. Any inference of efficacy or clinical significance should be interpreted with caution since the study was open-label and lacked a control group. These endpoints were only observed during the open-label extension study and were not prespecified endpoints in the randomized REGAIN study; therefore, they should be interpreted with caution.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information for SOLIRIS, including Boxed WARNING regarding serious meningococcal infections.
### Adverse events reported in REGAIN through week 26

Adverse events reported in ≥5% of patients treated with Soliris® (eculizumab) and at a greater frequency than patients treated with placebo in REGAIN.¹

<table>
<thead>
<tr>
<th>ADVERSE REACTION</th>
<th>SOLIRIS (n=62) n (%)</th>
<th>PLACEBO (n=63) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5 (8)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>5 (8)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>4 (7)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpes simplex virus infections</td>
<td>5 (8)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Injury, poisoning, and procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contusion</td>
<td>5 (8)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>9 (15)</td>
<td>5 (8)</td>
</tr>
</tbody>
</table>

**Adverse events reported in ≥5% of patients treated with Soliris® (eculizumab) and at a greater frequency than patients treated with placebo in REGAIN.¹**

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### Serious adverse events reported in the open-label extension study interim analysis⁵

**EVENT** | **EVENTS, n** | **PATIENTS EXPERIENCING AN EVENT, n (%)** | **EVENTS PER 100 PATIENT-YEARS** |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All serious adverse events</td>
<td>147</td>
<td>52 (44.4)</td>
<td>64.8</td>
</tr>
<tr>
<td>Most common (≥2 patients) MG- and infection-related serious adverse events ²⁻⁴</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MG⁵</td>
<td>28</td>
<td>15 (12.8)</td>
<td>12.3</td>
</tr>
<tr>
<td>Death</td>
<td>3</td>
<td>3 (2.6)</td>
<td>1.3</td>
</tr>
<tr>
<td>MG crisis</td>
<td>3</td>
<td>3 (2.6)</td>
<td>1.3</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3</td>
<td>3 (2.6)</td>
<td>1.3</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>3</td>
<td>3 (2.6)</td>
<td>1.3</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3</td>
<td>3 (2.6)</td>
<td>1.3</td>
</tr>
<tr>
<td>Sepsis</td>
<td>3</td>
<td>3 (2.6)</td>
<td>1.3</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>3</td>
<td>2 (1.7)</td>
<td>1.3</td>
</tr>
<tr>
<td>Influenza</td>
<td>2</td>
<td>2 (1.7)</td>
<td>0.9</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>2</td>
<td>2 (1.7)</td>
<td>0.9</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>3</td>
<td>2 (1.7)</td>
<td>1.3</td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
<td>2</td>
<td>2 (1.7)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Safety outcomes were evaluated in all patients during the open-label study

- The most common serious adverse event was MG worsening (12.8%)
- 1 nonfatal case of meningococcal infection was reported after data cutoff and was resolved with treatment
- 3 deaths had occurred by the time of interim analysis
  - Cause of death was attributed to chronic hepatic failure, pulmonary embolism, and multi-organ failure (hepatic failure as primary)

⁴Patient-years is the sum of all years for all patients, and observed event rate is the number of events per patient-year multiplied by 100.
⁵When a patient had more than 1 adverse event for a particular preferred term, that patient was counted only once for that preferred term.
¹Medical Dictionary for Regulatory Activities preferred term.
²Serious adverse events are adverse events that are life-threatening or result in death, hospitalization, or persistent or significant disability or incapacity, are congenital anomalies or birth defects, or are important medical events.
³Worsening (increased frequency and/or intensity) of a preexisting condition, including MG, is considered to be an adverse event.
⁴Please see additional Important Safety Information throughout and accompanying full Prescribing Information for SOLIRIS, including Boxed WARNING regarding serious meningococcal infections.
The most common adverse events in the open-label extension study interim analysis were consistent with REGAIN for up to 3 years.\textsuperscript{2,5}

<table>
<thead>
<tr>
<th>EVENT</th>
<th>EVENTS, n</th>
<th>PATIENTS EXPERIENCING AN EVENT, n (%)</th>
<th>EVENTS PER 100 PATIENT-YEARS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adverse events</td>
<td>1816</td>
<td>113 (96.6)</td>
<td>800.0</td>
</tr>
<tr>
<td>Most common adverse events,\textsuperscript{b} \ (&gt;10% of all patients, N=117)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>71</td>
<td>44 (37.6)</td>
<td>31.3</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>76</td>
<td>37 (31.6)</td>
<td>33.5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>40</td>
<td>27 (23.1)</td>
<td>17.6</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>55</td>
<td>27 (23.1)</td>
<td>24.2</td>
</tr>
<tr>
<td>MG\textsuperscript{d}</td>
<td>40</td>
<td>23 (19.7)</td>
<td>17.6</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>29</td>
<td>22 (18.8)</td>
<td>12.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>26</td>
<td>21 (17.9)</td>
<td>11.5</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>21</td>
<td>18 (15.4)</td>
<td>9.3</td>
</tr>
<tr>
<td>Cough</td>
<td>21</td>
<td>17 (14.5)</td>
<td>9.3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>21</td>
<td>17 (14.5)</td>
<td>9.3</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>32</td>
<td>17 (14.5)</td>
<td>14.1</td>
</tr>
<tr>
<td>Influenza</td>
<td>24</td>
<td>16 (13.7)</td>
<td>10.6</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>15</td>
<td>14 (12.0)</td>
<td>6.6</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>22</td>
<td>13 (11.1)</td>
<td>9.7</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>17</td>
<td>13 (11.1)</td>
<td>7.5</td>
</tr>
<tr>
<td>Fall</td>
<td>24</td>
<td>12 (10.3)</td>
<td>10.6</td>
</tr>
</tbody>
</table>

Safety outcomes were evaluated in all patients during the open-label study\textsuperscript{b}

- Infections were the most commonly reported events among the adverse events (AEs) of special interest\textsuperscript{c}
  - Prevalence of infections did not change with continued Soliris exposure

\textsuperscript{a}Patient-years is the sum of all years for all patients, and observed event rate is the number of events per patient-year multiplied by 100.

\textsuperscript{b}When a patient had more than 1 adverse event for a particular preferred term, that patient was counted only once for that preferred term.

\textsuperscript{c}Medical Dictionary for Regulatory Activities preferred term.

\textsuperscript{d}Worsening (increased frequency and/or intensity) of a preexisting condition, including MG, is considered to be an adverse event.

To see how Soliris works, visit solirisgmgpro.com/mechanism-of-action.
Consider Soliris® (eculizumab) to help improve symptom control for adult anti-AChR antibody-positive gMG patients who are inadequately controlled\textsuperscript{2,5}

- **Clinical Response\textsuperscript{1,2}**
  Available data suggest that clinical response was usually achieved by 12 weeks and sustained through the end of the 26-week REGAIN study.

- **Improved Activities of Daily Living\textsuperscript{2}**
  Mean improvement from baseline in MG-ADL score at week 26 in REGAIN study (-4.2 for Soliris vs -2.3 for placebo; \( P=0.006 \))

- **Improved Muscle Weakness\textsuperscript{2}**
  Mean improvement from baseline in QMG score at week 26 in REGAIN study (-4.6 for Soliris vs -1.6 for placebo; \( P=0.001 \))

- **Adverse Events\textsuperscript{1}**
  The most frequently reported adverse reaction in gMG placebo-controlled clinical trial (≥10%) is: musculoskeletal pain.

---

**SELECT IMPORTANT SAFETY INFORMATION**

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

Please see additional Important Safety Information throughout and accompanying full Prescribing Information for SOLIRIS, including Boxed WARNING regarding serious meningococcal infections.
WARNING: SERIOUS MENINGOCOCCAL INFECTIONS
See full prescribing information for complete boxed warning
Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris and may become rapidly life-threatening or fatal if not recognized and treated early (5.1).

• Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies (5.1).

• Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of Soliris, unless the risks of delaying Soliris therapy outweigh the risks of developing a meningococcal infection. (See Warnings and Precautions (5.1) for additional guidance on the management of the risk of meningococcal infection.)

• Vaccination reduces, but does not eliminate, the risk of meningococcal infections. Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.

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

INDICATIONS AND USAGE
Soliris is a complement inhibitor indicated for:

• The treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis (1.1).

• The treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (1.2).

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

• The treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AchR) antibody positive (1.3).

• The treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive (1.4).

DOSE AND ADMINISTRATION

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

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

CONTRAINDICATIONS
Soliris is contraindicated in:

• Patients with unresolved serious Neisseria meningitidis infection (4).

• Patients who are not currently vaccinated against Neisseria meningitidis, unless the risks of delaying Soliris treatment outweigh the risks of developing a meningococcal infection (5.1).

WARNINGS AND PRECAUTIONS

• Discontinue Soliris in patients who are being treated for serious meningococcal infections (5.1).

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

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

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 clinical trial (≥10%) are: upper respiratory infection, nasopharyngitis, diarrhea, back pain, dizziness, influenza, arthralgia, pharyngitis, and contusion (6.1).

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

See 17 PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2020

FULL PRESCRIBING INFORMATION: CONTENTS*
3  DOSAGE AND ADMINISTRATION
4  CONTRAINDICATIONS
5  WARNINGS AND PRECAUTIONS

1 INDICATIONS AND USAGE
1.1 Paroxysmal Nocturnal Hemoglobinuria (PNH)
1.2 Atypical Hemolytic Uremic Syndrome (aHUS)
1.3 Generalized Myasthenia Gravis (gMG)
1.4 Neuromyelitis Optica Spectrum Disorder (NMOSD)

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Vaccination and Prophylaxis
2.2 Recommended Dosage Regimen – PNH
2.3 Recommended Dosage Regimen – aHUS
2.4 Recommended Dosage Regimen – gMG and NMOSD
2.5 Dose Adjustment in Case of Plasmapheresis, Plasma Exchange, or Fresh Frozen Plasma Infusion
2.6 Preparation
2.7 Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
5.1 Serious Meningococcal Infections
5.2 Other Infections
5.3 Monitoring Disease Manifestations after Soliris Discontinuation
5.4 Thrombosis Prevention and Management
5.5 Infusion-Related Reactions

6 ADVERSE REACTIONS
6.1 Clinical Trial Experience
6.2 Immunogenicity
6.3 Postmarketing Experience

7 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use

8 FULL PRESCRIBING INFORMATION

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

• Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies (5.1).

• Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of Soliris, unless the risks of delaying Soliris therapy outweigh the risks of developing a meningococcal infection. (See Warnings and Precautions (5.1) for additional guidance on the management of the risk of meningococcal infection.)

• Vaccination reduces, but does not eliminate, the risk of meningococcal infections. Monitor patients for early signs of meningococcal infections and evaluate immediately if infection is suspected.

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

1 INDICATIONS AND USAGE
1.1 Paroxysmal Nocturnal Hemoglobinuria (PNH)
Soliris is indicated for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis.

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

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

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

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Vaccination and Prophylaxis
Vaccinate patients according to current ACIP guidelines to reduce the risk of serious infection (see Warnings and Precautions (5.1)). 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.

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

• 600 mg weekly for the first 4 weeks, followed by

• 900 mg for the fifth dose 1 week later, then
Dilute Soliris to a final concentration of 5 mg/mL by adding the appropriate amount (equal volume) of saline to the vial. Transfer the recommended dose to an infusion bag. 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 to Soliris to a final concentration of 5 mg/mL, by adding the appropriate amount (equal volume of diluent to drug volume) of 0.9% Sodium Chloride Injection, USP; 0.45% Sodium Chloride Injection, USP; 5% Dextrose in Water Injection, USP; or Ringer’s Injection, USP to the infusion bag.

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

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

<table>
<thead>
<tr>
<th>Patient Body Weight</th>
<th>Induction</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 kg and over</td>
<td>900 mg weekly x 4 doses</td>
<td>1200 mg at week 5; then 1200 mg every 2 weeks</td>
</tr>
<tr>
<td>30 kg to less than 40 kg</td>
<td>600 mg weekly x 2 doses</td>
<td>900 mg at week 3; then 900 mg every 2 weeks</td>
</tr>
<tr>
<td>20 kg to less than 30 kg</td>
<td>600 mg weekly x 2 doses</td>
<td>600 mg at week 3; then 600 mg every 2 weeks</td>
</tr>
<tr>
<td>10 kg to less than 20 kg</td>
<td>600 mg weekly x 1 dose</td>
<td>300 mg at week 2; then 300 mg every 2 weeks</td>
</tr>
<tr>
<td>5 kg to less than 10 kg</td>
<td>300 mg weekly x 1 dose</td>
<td>300 mg at week 2; then 300 mg every 3 weeks</td>
</tr>
</tbody>
</table>

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

**Table 2: Supplemental Dose of Soliris after PE/PI**

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

**3. DOSE FORMS AND STRENGTHS**

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

**4. CONTRAINDICATIONS**

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

**5. WARNINGS AND PRECAUTIONS**

**5.1 Serious Meningococcal Infections**

- Risk and Prevention
  - Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. The use of Soliris increases a patient’s susceptibility to serious meningococcal infections (septicaemia and/or meningitis). Soliris is associated with an approximate 2,000-fold increased risk of meningococcal disease in comparison to the general U.S. population annual rate (0.14 per 100,000 population in 2015).
  - Vaccinate for meningococcal disease according to the most current Advisory Committee on Immunization Practices (ACIP) recommendations for patients with complement deficiencies. Revaccinate patients in accordance with ACIP recommendations, considering the duration of Soliris therapy.
  - Immunize patients without a history of meningococcal vaccination at least 2 weeks prior to receiving the first dose of Soliris. If urgent Soliris therapy is indicated in an unvaccinated patient, administer meningococcal vaccine(s) as soon as possible and provide patients with two weeks of antibacterial drug prophylaxis.

In prospective clinical studies, 75/100 patients with aHUS were treated with Soliris less than 2 weeks after meningococcal vaccination and 64 of these 75 patients received antibiotics for prophylaxis of meningococcal infection until at least 2 weeks after meningococcal vaccination. The benefits and risks of antibiotic prophylaxis for prevention of meningococcal infections in patients receiving Soliris have not been established.

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

Closely monitor patients for early signs and symptoms of meningococcal infection and evaluate patients immediately if an infection is suspected. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early.

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

**5.2 Other Infections**

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

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

**5.3 Monitoring Disease Manifestations after Soliris Discontinuation**

**Treatment Discontinuation for PNH**

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

**Treatment Discontinuation for aHUS**

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

Clinical signs and symptoms of TMA include changes in mental status, seizures, angina, dyspnea, or thrombosis. In addition, the following changes in laboratory parameters may identify a TMA complication:

- Occurrence of two, or repeated measurement of any one of the following: a decrease in platelet count by 25% or more compared to baseline or the peak platelet count during Soliris treatment; an increase in serum creatinine by 25% or more compared to baseline or nadir during Soliris treatment; or, an increase in serum LDH by 25% or more over baseline or nadir during Soliris treatment.

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

**5.4 Thrombosis Prevention and Management**

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

**5.5 Infusion-Related Reactions**

Administration of Soliris may result in infusion-related reactions, including anaphylaxis or other hypersensitivity reactions. In clinical trials, no patients experienced an infusion-related reaction which required discontinuation of Soliris. Interrupt Soliris infusion and institute appropriate supportive measures if signs of cardiovascular instability or respiratory compromise occur.
6.1 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)].

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 5: Per Patient Incidence of Adverse Events in 10% or More Adult and Adolescent Patients

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

- Serious Meningococcal Infections [see Warnings and Precautions (5.1)]
- Other Infections [see Warnings and Precautions (5.2)]
- Monitoring Disease Manifestations after Soliris Discontinuation [see Warnings and Precautions (5.3)]
- Thrombosis Prevention and Management [see Warnings and Precautions (5.4)]
- Infusion-Related Reactions [see Warnings and Precautions (5.5)]
### 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=90)</th>
<th>12 to &lt;18 yrs (N=47)</th>
<th>Total (N=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></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><strong>Gastrointestinal Disorders</strong></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><strong>Infections and Infestations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infectiona</td>
<td>2 (40)</td>
<td>3 (30)</td>
<td>1 (25)</td>
<td>6 (32)</td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></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><strong>Cardiac Disorders</strong></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>
</tbody>
</table>

#### General Myasthenia Gravis (gMG)
- Includes the preferred terms upper respiratory tract infection and nasopharyngitis.

#### Infections and Infestations
- Upper respiratory tract infection includes upper respiratory infection and nasopharyngitis.

#### Gastrointestinal Disorders
- Diarrhea
- Vomiting

#### General Disorders and Administration Site Conditions
- Pyrexia

#### Respiratory, Thoracic and Mediastinal Disorders
- Cough
- Nasal congestion

#### Cardiac Disorders
- Tachycardia

---

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

<table>
<thead>
<tr>
<th>Number (%) of Patients</th>
<th>Soliris (N=96)</th>
<th>Placebo (N=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal pain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5 (8)</td>
<td>3 (5)</td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>5 (8)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>4 (7)</td>
<td>2 (3)</td>
</tr>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpes simplex virus infections</td>
<td>5 (8)</td>
<td>1 (2)</td>
</tr>
<tr>
<td><strong>Injury, Poisoning, and Procedural Complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contusion</td>
<td>5 (8)</td>
<td>2 (3)</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>9 (15)</td>
<td>5 (8)</td>
</tr>
</tbody>
</table>

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

---

### 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 uraemic syndrome (aHUS) in pregnancy (see Clinical Considerations). Animal studies using a mouse analogue of the Soliris molecule (murine anti-CS antibody) showed increased rates of developmental abnormalities and an increased rate of death and morbidity in non-human primates (NHP) at doses 2-8 times the human dose (see Data).

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

**Clinical Considerations**

- **Disease-associated maternal and/or fetal/neonatal risk**
- **PNH in pregnancy**
- **aHUS in pregnancy**

**Data**

**Human Data**

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

**Animal Data**

Animal reproduction studies were conducted in mice using doses of a murine anti-CS 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
Eculizumab, a complement inhibitor, is a recombinant humanized monoclonal IgG2/4 monoclonal antibody (mAb) that targets the human complement C5 protein. Eculizumab is a chimeric antibody containing human constant regions from human IgG2 sequences and human IgG4 sequences and murine variable regions. The humanized antibody has a molecular weight of approximately 148 kDa.

### 12.1 Mechanism of Action
Eculizumab acts by forming a disulfide-linked dimer and binds to the human C5 protein. In the complement membrane attack complex (MAC), it prevents the cleavage of C5 to C5a and C5b, thus inhibiting the formation of C5b-9. Once bound, eculizumab is internalized through the neonatal Fc receptor (FcRn) recycling mechanism of monoclonal antibodies such as eculizumab and thereby decreases serum eculizumab concentrations. Drug interactions have not been conducted with eculizumab in patients treated with warfarin.

### 13 NONCLINICAL TOXICOLGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenicity, mutagenicity, or impairment of fertility was observed in nonclinical studies. The safety and effectiveness of Soliris for the treatment of PNH, gMG, or NMOSD in pediatric patients have not been established.

### 8.2 Lactation

Ecumizumab crosses the placenta and is present in human milk. Available information is insufficient to inform the effect of eculizumab on breastfed infants. There are no data on the effects of eculizumab on milk production.

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

### Precautions (5.1, 5.2)

- **PK:** Renal function did not affect the pharmacokinetics of eculizumab in PNH (creatinine clearance of 6 mL/min to 396 mL/min calculated using Cockcroft-Gault formula), aHUS (estimated glomerular filtration rate [eGFR] of 5 mL/min/1.73 m² to 105 mL/min/1.73 m² using the Modification of Diet in Renal Disease [MDRD] formula), or gMG patients (eGFR of 44 mL/min/1.73 m² to 168 mL/min/1.73 m² using MDRD formula).

### Drug Interactions

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

### 14 CLINICAL STUDIES

#### 14.1 Paroxysmal Nocturnal Hemoglobinuria (PNH)

The safety and efficacy of Soliris in PNH patients with hemolysis were assessed in a randomized, double-blind, placebo-controlled 26-week study (PNH Study 1, NCT00122330). PNH patients were also treated with Soliris in a single arm 52 week study (PNH Study 2, NCT00122334) and in a long-term extension study (E501-001, NCT00122317). Patients received meningococcal vaccination prior to receipt of Soliris. In all studies, the dose of Soliris was 600 mg study drug every 7 days for 24 weeks, followed by 900 mg every 7 ± 2 days later, then 900 mg every 14 ± 2 days for the study duration. Soliris was administered as an intravenous infusion over 25 - 45 minutes.

#### 14.2 Pharmacodynamics

In the placebo-controlled study (PNH Study 1), Soliris at 900 mg every 2 weeks for 26 weeks reduced the absolute number of RBCs in the peripheral blood from a baseline of 3,674,000/µL to 3,091,000/µL (mean reduction of 16%). The percentage of RBCs with the PNH phenotype decreased from a baseline of 63% to 47% (mean decrease of 16%). These effects were seen among patients within each age group and with a variety of transfusion histories. The clinical benefit of these effects was seen as a reduction in the number of RBC transfusions required over the study duration. In addition, patients treated with Soliris had no adverse effects on mating or fertility.

#### 14.3 Pharmacokinetics

Following intravenous maintenance doses of 900 mg once every 2 weeks in patients with PNH, the week 26 observed mean ± SD serum eculizumab maximum concentration (Cmax) was 194 ± 76 mcg/mL, the trough concentration (Ctrough) was 97 ± 60 mcg/mL. Following intravenous maintenance doses of 1200 mg once every 2 weeks in patients with aHUS, the week 26 observed mean ± SD Cmax was 877 ± 331 and the Ctrough was 429 ± 188 mcg/mL. Following intravenous maintenance doses of 1200 mg once every 2 weeks in patients with gMG, the week 26 observed mean ± SD Cmax was 2,167 ± 877 and the Ctrough was 627 ± 212 mcg/mL. Following intravenous maintenance doses of 1200 mg once every 2 weeks in patients with NMOSD (N=44), the week 26 observed mean ± SD Cmax was 1,494 ± 816 and the Ctrough was 492 ± 213 mcg/mL. Following intravenous maintenance doses of 1200 mg once every 2 weeks in patients with NMOSD, the week 26 observed mean ± SD Cmax was 877 ± 331 and the Ctrough was 429 ± 188 mcg/mL.
A long-term extension study. All patients sustained a reduction in intravascular hemolysis over a total Soliris exposure time ranging from 10 to 54 months. There were fewer thrombotic events with Soliris treatment than during the same period of time prior to treatment. However, the majority of patients received concomitant anticoagulants; the effects of anticoagulant withdrawal during Soliris therapy was not studied [see Warnings and Precautions (5.4)].

14.2 Atypical Hemolytic Uremic Syndrome (aHUS)

Five single-arm studies [four prospective: C08-002A/B (NCT00844454 and NCT00844486), C08-003A/B (NCT00835893 and NCT00844408), C03-002 (NCT01900349), and C03-004 (NCT01190487); and one retrospective: C09-001 (NCT01770951)] evaluated the safety and efficacy of Soliris for the treatment of aHUS. Patients with aHUS received meningococcal vaccination prior to receipt of Soliris or received prophylactic treatment with antibiotics until 2 weeks after vaccination. In all studies, the dose of Soliris in adult and adolescent patients was 900 mg every 7 to 2 days for 4 weeks, followed by 1200 mg every 2 days later, then 1200 mg every 4 days for 14 to 2 days thereafter. The dosage regimens for pediatric patients weighing less than 40 kg enrolled in Study C09-001 and Study C01-003 was based on body weight [see Dosage and Administration (2.3)]. Efficacy evaluations were based on thrombomicroangiopathy (TMA) endpoints.

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

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

Renal function, as measured by eGFR, was improved and maintained during Soliris therapy. The mean eGFR (± SD) 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).

Reduction in terminal complement activity and an increase in platelet count relative to baseline were required dialysis at baseline were able to discontinue dialysis.

Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. Platelet counts were maintained at normal levels despite the elimination of PE/Pf. The mean platelet count (± SD) was 228 ± 78 x 10⁹/L at baseline, 233 ± 69 x 10⁹/L at week 26, and 224 ± 52 x 10⁹/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.

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

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study C08-003A/B</th>
<th>Study C08-003A/B at 2 yrs (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from aHUS diagnosis until screening in months, median (min, max)</td>
<td>0 (0, 0.36)</td>
<td>0 (0, 2)</td>
</tr>
<tr>
<td>Time from current clinical TMA manifestation until screening in months, median (min, max)</td>
<td>0 (0.07, 1.46)</td>
<td>&lt;1 (0, 2)</td>
</tr>
<tr>
<td>Platelet count (×10⁹/L), median (range)</td>
<td>12 (65)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Baseline LDH (UL), median (range)</td>
<td>328 (134, 634)</td>
<td>32 (12, 38)</td>
</tr>
<tr>
<td>eGFR improvement ≥15 mL/min/1.73 m², n (%)</td>
<td>0 (0, 0.36)</td>
<td>0 (0, 0.36)</td>
</tr>
<tr>
<td>Hematologic normalization, n (%)</td>
<td>0 (0, 0.36)</td>
<td>0 (0, 0.36)</td>
</tr>
<tr>
<td>Hematologic normalization, weeks (range)</td>
<td>32 (12, 38)</td>
<td>18 (90)</td>
</tr>
<tr>
<td>TMA-event free status, n (%)</td>
<td>32 (12, 38)</td>
<td>18 (90)</td>
</tr>
<tr>
<td>Daily TMA intervention rate, median (range)</td>
<td>18 (90)</td>
<td>18 (90)</td>
</tr>
<tr>
<td>Before eculizumab</td>
<td>18 (90)</td>
<td>18 (90)</td>
</tr>
<tr>
<td>Eculizumab treatment</td>
<td>18 (90)</td>
<td>18 (90)</td>
</tr>
</tbody>
</table>

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

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

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

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

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

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

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

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

The efficacy results for the aHUS retrospective study (Study C09-001r) were generally consistent with the results of the two prospective studies. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. Platelet counts were maintained at normal levels despite the elimination of PE/Pf. The mean platelet count (± SD) was 228 ± 78 x 10⁹/L at baseline, 233 ± 69 x 10⁹/L at week 26, and 224 ± 52 x 10⁹/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.

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

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

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Study C08-002A/B at 26 wks (N=20)</th>
<th>Study C08-003A/B at 2 yrs (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete TMA response, n (%)</td>
<td>13 (77)</td>
<td>8 (42)</td>
</tr>
<tr>
<td>Median duration of complete TMA response, weeks (range)</td>
<td>99 (25, 145)</td>
<td>99 (25, 145)</td>
</tr>
<tr>
<td>eGFR improvement ≥15 mL/min/1.73 m², n (%)</td>
<td>13 (77)</td>
<td>8 (42)</td>
</tr>
<tr>
<td>Hematologic normalization, n (%)</td>
<td>13 (77)</td>
<td>8 (42)</td>
</tr>
<tr>
<td>Hematologic normalization, weeks (range)</td>
<td>99 (25, 145)</td>
<td>99 (25, 145)</td>
</tr>
<tr>
<td>TMA-event free status, n (%)</td>
<td>13 (77)</td>
<td>8 (42)</td>
</tr>
<tr>
<td>Daily TMA intervention rate, median (range)</td>
<td>13 (77)</td>
<td>8 (42)</td>
</tr>
</tbody>
</table>

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

Reduction in terminal complement activity was observed in all patients after the commencement of Soliris. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. Platelet counts were maintained at normal levels despite the elimination of PE/Pf. The mean platelet count (± SD) was 228 ± 78 x 10⁹/L at baseline, 233 ± 69 x 10⁹/L at week 26, and 224 ± 52 x 10⁹/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.

14.2.1 Atypical Hemolytic Uremic Syndrome (aHUS)
Adult Patients with aHUS (Study C10-004)

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

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

<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>0.52 (0.03 – 19)</td>
</tr>
<tr>
<td>Time from current clinical TMA manifestation until first study dose in months, median (range)</td>
<td>125 (6 – 332)</td>
<td>375 (131 – 3318)</td>
</tr>
</tbody>
</table>

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

Study C10-003 enrolled patients who were required to have a platelet count < lower limit of normal range (LLN), evidence of hemolysis such as an elevation in serum LDH above the upper limits of normal, serum creatinine level ≥97 percentile for age without the need for chronic dialysis. The median patient age was 35 (range: 18 to 80 years). All patients enrolled in Study C10-003 were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 38%-121%. Fifty percent of patients with and without identified mutations in genes encoding complement regulatory factor proteins or auto-antibodies to factor H.

### Table 18: Efficacy Results for Study C10-004

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Study C10-004 (N=41)</th>
<th>Study C10-003 (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete TMA response, n (%)</td>
<td>23 (56)</td>
<td>11 (50)</td>
</tr>
<tr>
<td>95% CI</td>
<td>40.72</td>
<td>19.25</td>
</tr>
<tr>
<td>Median duration of complete TMA response, weeks (range)</td>
<td>42 (6, 75)</td>
<td>40 (14, 77)</td>
</tr>
<tr>
<td>Patients with eGFR improvement ≥ 15 mL/min/1.73m², n (%)</td>
<td>22 (54)</td>
<td>11 (50)</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>40 (14, 77)</td>
</tr>
<tr>
<td>TMA Event-Free Status, n (%)</td>
<td>37 (90)</td>
<td>38 (14, 77)</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></td>
<td></td>
</tr>
<tr>
<td>On eculizumab treatment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Study C10-003 enrolled patients who were required to have a platelet count < lower limit of normal range (LLN), evidence of hemolysis such as an elevation in serum LDH above the upper limits of normal, serum creatinine level ≥97 percentile for age without the need for chronic dialysis. The median patient age was 35 (range: 18 to 80 years). All patients enrolled in Study C10-003 were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 38%-121%. Fifty percent of patients had an identified complement regulatory factor mutation or auto-antibody. A total of 10 patients received PE/PI prior to eculizumab. Table 19 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in Study C10-003.

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

<table>
<thead>
<tr>
<th>Parameter</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>0.51 (0.03 – 58)</td>
</tr>
<tr>
<td>Time from current clinical TMA manifestation until first study dose in months, median (range)</td>
<td>0.23 (0.3 – 4)</td>
</tr>
<tr>
<td>Baseline platelet count (x 10^12/L), median (range)</td>
<td>110 (19-146)</td>
</tr>
<tr>
<td>Baseline LDH (U/L), median (range)</td>
<td>1510 (282-7164)</td>
</tr>
</tbody>
</table>

Patients in Study C10-003 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 of the 24 patients who required dialysis at study baseline were able to discontinue dialysis during Soliris treatment.

### 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>Complete hematologic normalization, n (%)</td>
<td>14 (78)</td>
<td>15 (82)</td>
</tr>
<tr>
<td>Median duration of complete hematologic normalization, weeks (range)</td>
<td>38 (14, 77)</td>
<td>38 (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>Before eculizumab treatment</td>
<td>0.2 (0.7)</td>
</tr>
<tr>
<td>On eculizumab treatment</td>
<td>0.0 (0.91)</td>
<td></td>
</tr>
</tbody>
</table>

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

Study C10-003 enrolled patients who were required to have a platelet count < lower limit of normal range (LLN), evidence of hemolysis such as an elevation in serum LDH above the upper limits of normal, serum creatinine level ≥97 percentile for age without the need for chronic dialysis. The median patient age was 35 (range: 18 to 80 years). All patients enrolled in Study C10-003 were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 38%-121%. Fifty percent of patients had an identified complement regulatory factor mutation or auto-antibody. A total of 10 patients received PE/PI prior to eculizumab. Table 19 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in Study C10-003.

### Table 21: Analysis of Change from Baseline to Week 26 in MG-ADL and QMG 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>MG-ADL</td>
<td>-4.2 (0.49)</td>
<td>-2.3 (0.48)</td>
<td>-1.9 (-3.3, -0.6)</td>
<td>0.006* (0.014)</td>
</tr>
<tr>
<td>p-values</td>
<td>-4.6 (0.60)</td>
<td>-1.6 (0.59)</td>
<td>-3.0 (-4.6, -1.3)</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 Week 26 using a repeated measure analysis; b: in ranks at Week 26 using a worst case analysis). In gMG Study 1, a clinical response was defined in the MG-ADL total score as at least a 3-point improvement and in MG 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. Both markedly higher for gMG compared to placebo. At higher thresholds (4-, 5-, 6-, 7-, and 8-point improvement on MG-ADL, and 6-, 7-, 8-, 9-, and 10-point improvement on QMG, the proportion of clinical responders was consistently greater for Soliris compared to placebo. Available data suggest that clinical response is usually achieved by 12 weeks of Soliris treatment.

14.4 Neuromyelitis Optica Spectrum Disorder (NMO/SD)

The efficacy of Soliris for the treatment of NMO/SD was established in NMO/SD Study 1 (NCT01982345), a randomized, double-blind, placebo-controlled trial that enrolled 143 patients with NMO/SD 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. 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).

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

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

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

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

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

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

<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*</td>
<td>Rate ratio (eculizumab/placebo)</td>
<td>…</td>
<td>0.045</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>…</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Based on a Poisson regression adjusted for randomization strata and historical ARR in 24 months prior to screening.

ARR = annualized relapse rate

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Soliris (eculizumab) injection is a sterile, preservative-free, clear, colorless solution supplied as one 300 mg/30 mL (10 mg/mL) single-dose vial per carton (NDC 255682-001-01).

Store Soliris vials refrigerated at 2°-8° C (36°-46°F) in the original carton to protect from light until time of use. Do not use past the expiration date stamped on the vial. Do not re-freeze the product.

17 PATIENT COUNSELING INFORMATION

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

Meningococcal infection

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

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

Signs and Symptoms of Meningococcal Infection

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

These signs and symptoms are as follows:

- headache with a stiff neck or stiff back
- fever
- 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 they should be vaccinated against Streptococcus pneumoniae and Haemophilus influenzae type b (Hib) according to current medical guidelines.

Infusion-Related Reactions

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

Discontinuation

Inform patients with PHN that they may develop hemorrhage during PHN when Soliris is discontinued and that they will be monitored by their healthcare professional for at least 8 weeks following Soliris discontinuation.

Inform patients with aHUS that there is a potential for TMA complications due to aHUS when Soliris is discontinued and that they will be monitored by their healthcare professional for at least 12 weeks following Soliris discontinuation.

Inform patients who discontinue Soliris to keep the Soliris Patient Safety Information Card with them for three months after the last Soliris dose, because the increased risk of meningococcal infection persists for several weeks following discontinuation of Soliris.

Manufactured by:

Alexion Pharmaceuticals, Inc.

121 Seaport Boulevard

Boston, MA 02210 USA

US License Number 1743

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

MEDICATION GUIDE

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

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

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

- SOLIRIS increases your chance of getting serious and life-threatening meningococcal infections. Meningococcal infections may quickly become life-threatening and cause death if not recognized and treated early.

1. You must receive meningococcal vaccines at least 2 weeks before your first dose of SOLIRIS if you have not already had this vaccine.

2. If you or 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 vaccinations.

1. You should also receive two weeks of antibiotics with your vaccinations.

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

What is SOLIRIS?
SOLIRIS is a prescription medicine called a monoclonal antibody. SOLIRIS is used to treat:
• patients- with a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH).
• adults and children with a disease called atypical Hemolytic Uremic Syndrome (aHUS).
SOLIRIS is not for use in treating people with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).
• adults with a disease called generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AcHR) antibody positive
• adults with a disease called neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody positive.
It is not known if SOLIRIS is safe and effective in children with PNH, gMG, or NMOSD.

Who should not receive SOLIRIS?
Do not receive SOLIRIS if you:
• have a meningococcal infection.
• have not been vaccinated against meningitis infection unless your doctor decides that urgent treatment with SOLIRIS is needed. See “What is the most important information I should know about SOLIRIS?”

Before you receive SOLIRIS, tell your doctor about all of your medical conditions, including if you:
• have an infection or fever.
• are pregnant or plan to become pregnant. It is not known if SOLIRIS will harm your unborn baby.
• are breastfeeding or plan to breastfeed. It is not known if SOLIRIS passes into your breast milk.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. SOLIRIS and other medicines can affect each other causing side effects.
It is important that you:
• have all recommended vaccinations before you start SOLIRIS.
• receive 2 weeks of antibiotics if you immediately start SOLIRIS.
• stay up-to-date with all recommended vaccinations during treatment with SOLIRIS.

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

How should I receive SOLIRIS?
SOLIRIS is given through a vein (I.V. or intravenous infusion) usually over 35 minutes in adults and 1 to 4 hours in pediatric patients. If you have an infusion-related reaction during your SOLIRIS infusion, your doctor may decide to give SOLIRIS more slowly or stop your infusion.
• If you are an adult, you will usually receive a SOLIRIS infusion by your doctor:
  ° weekly for five weeks, then
  ° every 2 weeks
• If you are less than 18 years of age, your doctor will decide how often you will receive SOLIRIS depending on your age and body weight
• After each infusion, you should be monitored for one hour for infusion-related reactions. See “What are the possible side effects of SOLIRIS?”
• If you miss a SOLIRIS infusion, call your doctor right away.
• If you have PNH, your doctor will need to monitor you closely for at least 8 weeks after stopping SOLIRIS. Stopping treatment with SOLIRIS may cause breakdown of your red blood cells due to PNH.

Symptoms or problems that can happen due to red blood cell breakdown include:
• drop in the number of your red blood cell count
• drop in your platelet counts
• kidney problems
• blood clots
• chest pain
If you have aHUS, your doctor will need to monitor you closely during and for at least 12 weeks after stopping treatment for signs of worsening aHUS symptoms or problems related to abnormal clotting (thrombotic microangiopathy).

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

What are the possible side effects of SOLIRIS?
SOLIRIS can cause serious side effects including:
• See “What is the most important information I should know about SOLIRIS?”
• Serious infusion-related reactions. Serious infusion-related reactions can happen during your SOLIRIS infusion. Tell your doctor or nurse right away if you get any of these symptoms during your SOLIRIS infusion:
  ° chest pain
  ° trouble breathing or shortness of breath
  ° swelling of your face, tongue, or throat
  ° feel faint or pass out
If you have an infusion-related reaction to SOLIRIS, your doctor may need to infuse SOLIRIS more slowly, or stop SOLIRIS. See “How will I receive SOLIRIS?”

The most common side effects in people with PNH treated with SOLIRIS include:
• headache
• pain or swelling of your nose or throat (nasopharyngitis)
• back pain
• nausea
• low red blood cell count (anemia)
• cough
• swelling of legs or feet (peripheral edema)

The most common side effects in people with aHUS treated with SOLIRIS include:
• headache
• diarrhea
• high blood pressure (hypertension)
• common cold (upper respiratory infection)
• stomach-area (abdominal pain)
• vomiting
• pain or swelling of your nose or throat (nasopharyngitis)
• muscle and joint (musculoskeletal) pain
• joint pain (arthritis)
• stomach area (abdominal pain)
• fever
• flu like symptoms (influenza)
• cough, sore throat, and body aches
• difficulty breathing
• throat irritation (pharyngitis)
• bruising (contusion)

Tell your doctor about any side effect that bothers you or that does not go away. These are not all the possible side effects of SOLIRIS. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

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

What are the ingredients in SOLIRIS?
Active ingredient: eculizumab
Inactive ingredients: polysorbate 80 (vegetable origin), sodium chloride, sodium phosphate dibasic, sodium phosphate monobasic, and Water for Injection

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