

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Soliris safely and effectively. See full prescribing information for Soliris.

Soliris® (eculizumab)

Concentrated solution for intravenous infusion  
Initial U.S. Approval: 2007

### WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

See full prescribing information for complete boxed warning

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. Meningococcal infection 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.
- Immunize patients with a meningococcal vaccine 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* (5.1) for additional guidance on the management of the risk of meningococcal infection.)
- 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 (5.2). Enrollment in the Soliris REMS program and additional information are available by telephone: 1-888-SOLIRIS (1-888-765-4747).

### RECENT MAJOR CHANGES

|   |        |
|---|--------|
| Box Warning                                 | 9/2011 |
| Indications and Usage (1.2)                 | 9/2011 |
| Contraindications (4)                       | 9/2011 |
| Dosage and Administration (2.2)             | 9/2011 |
| Warnings and Precautions (5.3, 5.4 and 5.6) | 9/2011 |
| Adverse Reactions (6.1)                     | 9/2011 |
| Use in Specific Populations (8.4)           | 9/2011 |
| Clinical Studies (14.2)                     | 9/2011 |
| Patient Counseling Information (17)         | 9/2011 |

### 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).  
The effectiveness of Soliris in aHUS is based on the effects on thrombotic microangiopathy (TMA) and renal function.

Prospective clinical trials in additional patients are ongoing to confirm the benefit of Soliris in patients with aHUS.

### Limitation of Use

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

### DOSAGE AND ADMINISTRATION

Only administer as an intravenous infusion

PNH Dosage Regimen: (2.1)  
aHUS Dosage Regimen: (2.2)

### DOSAGE FORMS AND STRENGTHS

300 mg single-use vials each containing 30 mL of 10 mg/mL sterile, preservative-free solution (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.
- Use caution when administering Soliris to patients with any other systemic infection (5.2).

### ADVERSE REACTIONS

The most frequently reported adverse reactions in the PNH randomized trial ( $\geq 10\%$  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 ( $\geq 15\%$  combined per patient incidence) are: hypertension, upper respiratory tract infection, diarrhea, headache, anemia, vomiting, nausea, urinary tract infection, and leukopenia (6.1).

### USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, Soliris may cause fetal harm (8.1).  
Nursing Mothers: Caution should be exercised when administered to a nursing woman (8.3).  
Pediatric Use: PNH: safety and effectiveness not established. aHUS: safety and effectiveness similar to adult patients (8.4).

To report SUSPECTED ADVERSE REACTIONS, contact Alexion Pharmaceuticals, Inc. at 1-888-SOLIRIS (1-888-765-4747) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

See 17 PATIENT COUNSELING INFORMATION and the FDA-approved Medication Guide.

Revised: 09/2011

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## 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 (5.1).

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.
- Immunize patients with a meningococcal vaccine 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 (5.1)* for additional guidance on the management of the risk of meningococcal infection.)
- 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 (5.2). Enrollment in the Soliris REMS program and additional information are available by telephone: 1-888-SOLIRIS (1-888-765-4747).

## **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.

The effectiveness of Soliris in aHUS is based on the effects on thrombotic microangiopathy (TMA) and renal function. Prospective clinical trials in additional patients are ongoing to confirm the benefit of Soliris in patients with aHUS.

#### Limitation of Use

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

## 2 DOSAGE AND ADMINISTRATION

Healthcare professionals who prescribe Soliris must enroll in the Soliris REMS. [*see Warnings and Precautions (5.2)*].

Vaccinate patients according to current ACIP guidelines to reduce the risk of serious infection. [*see Warnings and Precautions (5.1) and (5.2)*].

**Only administer as an intravenous infusion.**

### 2.1 Recommended Dosage Regimen - PNH

**Soliris therapy consists of:**

- 600 mg weekly for the first 4 weeks, followed by
- 900 mg for the fifth dose 1 week later, then
- 900 mg every 2 weeks thereafter.

Soliris should be administered at the recommended dosage regimen time points, or within two days of these time points [*see Warnings and Precautions (5.6)*].

### 2.2 Recommended Dosage Regimen - aHUS

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

- 900 mg weekly for the first 4 weeks, followed by
- 1200 mg for the fifth dose 1 week later, then
- 1200 mg every 2 weeks thereafter.

**For patients less than 18 years of age, administer Soliris based upon body weight, according to the following schedule (Table 1):**

**Table 1: Dosing recommendations in patients less than 18 years of age**

| Patient Body Weight      | Induction               | Maintenance                                      |
|--------------------------|-------------------------|--|
| 40 kg and over           | 900 mg weekly x 4 doses | 1200 mg at week 5;<br>then 1200 mg every 2 weeks |
| 30 kg to less than 40 kg | 600 mg weekly x 2 doses | 900 mg at week 3;<br>then 900 mg every 2 weeks   |
| 20 kg to less than 30 kg | 600 mg weekly x 2 doses | 600 mg at week 3;<br>then 600 mg every 2 weeks   |
| 10 kg to less than 20 kg | 600 mg weekly x 1 dose  | 300 mg at week 2;<br>then 300 mg every 2 weeks   |

|                         |                        |  |
|-------------------------|------------------------|--|
| 5 kg to less than 10 kg | 300 mg weekly x 1 dose | 300 mg at week 2;<br>then 300 mg every 3 weeks |
|-------------------------|------------------------|--|

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

Supplemental dosing of Soliris is required in the setting of concomitant support with PE/PI (plasmapheresis or plasma exchange; or fresh frozen plasma infusion) (Table 2).

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

| Type of Intervention              | Most Recent Soliris Dose | Supplemental Soliris Dose With Each PE/PI Intervention    | Timing of Supplemental Soliris Dose                             |
|-----------------------------------|--------------------------|---|---|
| Plasmapheresis or plasma exchange | 300 mg                   | 300 mg per each plasmapheresis or plasma exchange session | Within 60 minutes after each plasmapheresis or plasma exchange  |
|                                   | 600 mg or more           | 600 mg per each plasmapheresis or plasma exchange session |   |
| Fresh frozen plasma infusion      | 300 mg or more           | 300 mg per each unit of fresh frozen plasma               | 60 minutes prior to each 1 unit of fresh frozen plasma infusion |

### 2.3 Preparation and Administration

Soliris must be diluted to a final admixture concentration of 5 mg/mL using the following steps:

- Withdraw the required amount of Soliris from the vial into a sterile syringe.
- Transfer the recommended dose to an infusion bag.
- Dilute Soliris to a final concentration of 5 mg/mL by adding the appropriate amount (equal volume of diluent to drug volume) of 0.9% Sodium Chloride Injection, USP; 0.45% Sodium Chloride Injection, USP; 5% Dextrose in Water Injection, USP; or Ringer’s Injection, USP to the infusion bag.

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

**Table 3: Preparation and Reconstitution of Soliris**

| <b>Soliris Dose</b> | <b>Diluent Volume</b> | <b>Final Volume</b> |
|---------------------|-----------------------|---------------------|
| 300 mg              | 30 mL                 | 60 mL               |
| 600 mg              | 60 mL                 | 120 mL              |
| 900 mg              | 90 mL                 | 180 mL              |
| 1200 mg             | 120 mL                | 240 mL              |

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

Prior to administration, the admixture should be allowed to adjust to room temperature [18°-25° C, 64-77° F]. The admixture must not be heated in a microwave or with any heat source other than ambient air temperature. The Soliris admixture should be inspected visually for particulate matter and discoloration prior to administration.

## **2.4 Administration**

### *Do Not Administer As An Intravenous Push or Bolus Injection*

The Soliris admixture should be administered by intravenous infusion over 35 minutes via gravity feed, a syringe-type pump, or an infusion pump. Admixed solutions of Soliris are stable for 24 hours at 2-8° C (36-46° F) and at room temperature.

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

## **3 DOSAGE FORMS AND STRENGTHS**

Soliris is supplied as 300 mg single-use vials each containing 30 mL of 10 mg/mL sterile, preservative-free eculizumab solution.

## **4 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 [see *Warnings and Precautions (5.1)*].

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Serious Meningococcal Infections**

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

Administer a polyvalent meningococcal vaccine 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.

Vaccinate 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 the meningococcal vaccine as soon as possible. In clinical studies, 33/67 patients with aHUS were treated with Soliris less than 2 weeks after meningococcal vaccination and 31 of these 33 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, a previously vaccinated patient with aHUS developed meningococcal sepsis during the post-study follow-up period [*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 Soliris REMS**

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

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

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

### **5.3 Other Infections**

Soliris blocks terminal complement activation; therefore patients may have increased susceptibility to infections, especially with encapsulated bacteria. 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.

### **5.4 Monitoring 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 studies, 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 reinstatement of Soliris treatment, plasma therapy [plasmapheresis, plasma exchange, or fresh frozen plasma infusion (PE/PI)], or appropriate organ-specific supportive measures.

### **5.5 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.

### **5.6 Laboratory Monitoring**

#### PNH

Serum LDH levels increase during hemolysis and may assist in monitoring Soliris effects, including the response to discontinuation of therapy. In clinical studies, six patients achieved a reduction in serum LDH levels only after a decrease in the Soliris dosing interval from 14 to 12 days. All other patients achieved a reduction in serum LDH levels with the 14 day dosing interval [see *Clinical Pharmacology (12.2)* and *Clinical Studies (14.1)*].

## aHUS

Early signs of thrombotic microangiopathy (TMA) include a decrease in platelet count, and increases in serum LDH and creatinine levels. Follow patients for signs of TMA by monitoring serial platelet counts, serum LDH, and creatinine during Soliris therapy and following discontinuation of Soliris.

### **5.7 Infusion Reactions**

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

## **6 ADVERSE REACTIONS**

### **6.1 Clinical Trial Experience**

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

## PNH

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

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

**Table 4: Adverse Reactions Reported In 5% Or More Of Soliris Treated Patients And Greater Than Placebo In The Controlled Clinical Study**

| Reaction | Soliris<br>N = 43<br>N (%) | Placebo<br>N = 44<br>N (%) |
|----------|----------------------------|----------------------------|
|----------|----------------------------|----------------------------|

|                             |         |         |
|-----------------------------|---------|---------|
| Headache                    | 19 (44) | 12 (27) |
| Nasopharyngitis             | 10 (23) | 8 (18)  |
| Back pain                   | 8 (19)  | 4 (9)   |
| Nausea                      | 7 (16)  | 5 (11)  |
| Fatigue                     | 5 (12)  | 1 (2)   |
| Cough                       | 5 (12)  | 4 (9)   |
| Herpes simplex infections   | 3 (7)   | 0       |
| Sinusitis                   | 3 (7)   | 0       |
| Respiratory tract infection | 3 (7)   | 1 (2)   |
| Constipation                | 3 (7)   | 2 (5)   |
| Myalgia                     | 3 (7)   | 1 (2)   |
| Pain in extremity           | 3 (7)   | 1 (2)   |
| Influenza-like illness      | 2 (5)   | 1 (2)   |

In the placebo-controlled clinical study, serious adverse reactions occurred among 4 (9%) patients receiving Soliris and 9 (21%) patients receiving placebo. The serious reactions included infections and progression of PNH. No deaths occurred in the study and no patients receiving Soliris experienced a thrombotic event; one thrombotic event occurred in a patient receiving placebo.

Among 193 patients with PNH treated with Soliris in the single arm, clinical study or the follow-up study, the adverse reactions were similar to those reported in the placebo-controlled clinical study. Serious adverse reactions occurred among 16% of the patients in these studies. The most common serious adverse reactions were: viral infection (2%), headache (2%), anemia (2%), and pyrexia (2%).

### aHUS

The safety of Soliris therapy in patients with aHUS was evaluated in two prospective, single-arm studies (aHUS Studies 1 and 2) and one retrospective study (aHUS Study 3). The data described below were derived from 37 adult and adolescent patients with aHUS enrolled in aHUS Study 1 and aHUS Study 2. All patients received the recommended dosage of Soliris. Median exposure was 38 weeks (range: 2-64 weeks).

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. Table 5 summarizes all adverse events reported in at least 10% of patients in aHUS Studies 1 and 2 combined.

**Table 5: Per Patient Incidence of Adverse Events in Adult and Adolescent Patients Enrolled in aHUS Study 1 and aHUS Study 2 Separately and in Total**

| MedDRA ver. 11.0 | Number (%) of Patients |                |              |
|------------------|------------------------|----------------|--------------|
|                  | Study 1 (n=17)         | Study 2 (n=20) | Total (n=37) |

| MedDRA ver. 11.0  | Number (%) of Patients |                |              |
|---|------------------------|----------------|--------------|
|   | Study 1 (n=17)         | Study 2 (n=20) | Total (n=37) |
| <b>Vascular Disorders</b>                                   |                        |                |              |
| Hypertension <sup>a</sup>                                   | 8(47)                  | 5 (25)         | 13 (35)      |
| <b>Infections and Infestations</b>                          |                        |                |              |
| Upper respiratory tract infection <sup>b</sup>              | 5 (29)                 | 8 (40)         | 13(35)       |
| Urinary tract infection                                     | 4 (24)                 | 2 (10)         | 6 (16)       |
| <b>Gastrointestinal Disorders</b>                           |                        |                |              |
| Diarrhea  | 6 (35)                 | 6 (30)         | 12 (32)      |
| Vomiting  | 5 (29)                 | 3 (15)         | 8 (22)       |
| Nausea  | 4 (24)                 | 3 (15)         | 7 (19)       |
| Abdominal pain  | 0                      | 4 (20)         | 4 (11)       |
| <b>Nervous System Disorders</b>                             |                        |                |              |
| Headache  | 7 (41)                 | 4 (20)         | 11 (30)      |
| <b>Blood and Lymphatic System Disorders</b>                 |                        |                |              |
| Anemia  | 6 (35)                 | 3 (15)         | 9 (24)       |
| Leukopenia  | 4 (24)                 | 2 (10)         | 6 (16)       |
| <b>Psychiatric Disorders</b>                                |                        |                |              |
| Insomnia  | 4 (24)                 | 1 (5)          | 5 (14)       |
| <b>Respiratory, Thoracic and Mediastinal Disorders</b>      |                        |                |              |
| Cough   | 2 (12)                 | 3 (15)         | 5 (14)       |
| Pharyngolaryngeal pain                                      | 1 (6)                  | 4 (20)         | 5 (14)       |
| <b>General Disorders and Administration Site Conditions</b> |                        |                |              |
| Fatigue   | 3 (18)                 | 1 (5)          | 4 (11)       |
| Peripheral edema  | 3 (18)                 | 1 (5)          | 4 (11)       |
| Pyrexia   | 3 (18)                 | 1 (5)          | 4 (11)       |
| <b>Ear and Labyrinth Disorders</b>                          |                        |                |              |
| Vertigo   | 1 (6)                  | 3 (15)         | 4 (11)       |
| <b>Musculoskeletal and Connective Tissue Disorders</b>      |                        |                |              |
| Pain in extremity   | 1 (6)                  | 3 (15)         | 4 (11)       |

<sup>a.</sup> includes the preferred terms hypertension, accelerated hypertension, and malignant hypertension.

<sup>b.</sup> includes the preferred terms upper respiratory tract infection and nasopharyngitis.

In aHUS Studies 1 and 2 combined, 54% (20/37) of patients experienced a serious adverse event (SAE). The most commonly reported SAEs were hypertension (16%) and infections (14%). One patient discontinued Soliris due to adverse events deemed unrelated to Soliris.

Analysis of retrospectively collected adverse event data from pediatric and adult patients enrolled in aHUS Study 3 (N=30) revealed a safety profile that was similar to that which was observed in the two prospective studies. aHUS Study 3 included 19 pediatric patients less than 18 years of age. Overall, the safety of Soliris in pediatric patients with aHUS

enrolled in Study 3 appeared similar to that observed in adult patients. The most common ( $\geq 15\%$ ) adverse events occurring in pediatric patients are presented in Table 6.

**Table 6: Adverse Reactions Occurring in at Least 15% of Patients Less than 18 Years of Age Enrolled in aHUS Study 3**

| MedDRA ver. 11.0  | Number (%) of Patients |                         |                        | Total<br>(n=19) |
|---|------------------------|-------------------------|------------------------|-----------------|
|   | < 2 yrs<br>(n=5)       | 2 to < 12 yrs<br>(n=10) | 12 to <18 yrs<br>(n=4) |                 |
| <b>General Disorders and Administration Site Conditions</b> |                        |                         |                        |                 |
| Pyrexia   | 4 (80)                 | 4 (60)                  | 1 (25)                 | 9 (47)          |
| <b>Gastrointestinal Disorders</b>                           |                        |                         |                        |                 |
| Diarrhea  | 1 (20)                 | 4 (40)                  | 1 (25)                 | 6 (32)          |
| Vomiting  | 2 (40)                 | 1 (10)                  | 1 (25)                 | 4 (21)          |
| <b>Infections and Infestations</b>                          |                        |                         |                        |                 |
| Upper respiratory tract infection <sup>a</sup>              | 2 (40)                 | 3 (30)                  | 1 (25)                 | 6 (32)          |
| <b>Respiratory, Thoracic and Mediastinal Disorders</b>      |                        |                         |                        |                 |
| Cough   | 3 (60)                 | 2 (20)                  | 0 (0)                  | 5 (26)          |
| Nasal congestion  | 2 (40)                 | 2 (20)                  | 0 (0)                  | 4 (21)          |
| <b>Cardiac Disorders</b>                                    |                        |                         |                        |                 |
| Tachycardia   | 2 (40)                 | 2 (20)                  | 0 (0)                  | 4 (21)          |

<sup>a</sup> includes the preferred terms upper respiratory tract infection and nasopharyngitis.

## 6.2 Immunogenicity

As with all proteins there is a potential for immunogenicity. The immunogenicity of Soliris has been evaluated using two different immunoassays for the detection of anti-eculizumab antibodies: a direct enzyme-linked immunosorbent assay (ELISA) using the Fab fragment of eculizumab as target was used for the PNH indication; and an electrochemiluminescence (ECL) bridging assay using the eculizumab whole molecular as target was used for the aHUS indication. Low titers of antibodies to Soliris were detected in 3/196 (2%) of all PNH patients treated with Soliris by the ELISA assay. In patients with aHUS treated with Soliris, antibodies to Soliris were detected in 1/37 (2.7%) by the ECL assay. An ECL based neutralizing HAHA assay with a low sensitivity of 2 mcg/mL was performed to detect neutralizing antibodies for the 37 patients with aHUS. No neutralizing activity to Soliris was detected in patients with aHUS treated with Soliris. No apparent correlation of antibody development to clinical response was observed in both indications. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to Soliris in an ELISA based assay and/or an ECL based assay are highly dependent on the sensitivity and specificity of the assay used. Additionally, the observed incidence of antibody positivity in the assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the

incidence of antibodies to Soliris with the incidence of antibodies to other products may be misleading.

### **6.3 Postmarketing Experience**

Cases of serious or fatal meningococcal infections have been reported.

## **7 DRUG INTERACTIONS**

Drug interaction studies have not been performed with Soliris.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

Pregnancy Category C:

There are no adequate and well-controlled studies of Soliris in pregnant women. Soliris, a recombinant IgG molecule (humanized anti-C5 antibody), is expected to cross the placenta. Animal studies using a mouse analogue of the Soliris molecule (murine anti-C5 antibody) showed increased rates of developmental abnormalities and an increased rate of dead and moribund offspring at doses 2-8 times the human dose. Soliris should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal reproduction studies were conducted in mice using doses of a murine anti-C5 antibody that approximated 2-4 times (low dose) and 4-8 times (high dose) the recommended human Soliris dose, based on a body weight comparison. When animal exposure to the antibody occurred in the time period from before mating until early gestation, no decrease in fertility or reproductive performance was observed. When maternal exposure to the antibody occurred during organogenesis, two cases of retinal dysplasia and one case of umbilical hernia were observed among 230 offspring born to mothers exposed to the higher antibody dose; however, the exposure did not increase fetal loss or neonatal death. When maternal exposure to the antibody occurred in the time period from implantation through weaning, a higher number of male offspring became moribund or died (1/25 controls, 2/25 low dose group, 5/25 high dose group). Surviving offspring had normal development and reproductive function.

### **8.3 Nursing Mothers**

It is not known whether Soliris is excreted into human milk. IgG is excreted in human milk, so it is expected that Soliris will be present in human milk. However, published data suggest that antibodies in human milk do not enter the neonatal and infant circulation in substantial amounts. Caution should be exercised when Soliris is administered to a nursing woman. The unknown risks to the infant from gastrointestinal or limited systemic exposure to Soliris should be weighed against the known benefits of human milk feeding.

## 8.4 Pediatric Use

The safety and effectiveness of Soliris for the treatment of PNH in pediatric patients below the age of 18 years have not been established.

Three clinical studies assessing the safety and effectiveness of Soliris for the treatment of aHUS included a total of 25 pediatric patients (ages 2 months to 17 years). The safety and effectiveness of Soliris for the treatment of aHUS appear similar in pediatric and adult patients [see *Dosage and Administration* (2.2), *Adverse Reactions* (6.1), and *Clinical Studies* (14.2)].

Administer vaccinations for the prevention of infection due to *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) according to ACIP guidelines [see *Warnings and Precautions* (5.1, 5.2)].

## 8.5 Geriatric Use

Sixteen patients 65 years of age or older (15 with PNH and 1 with aHUS) were treated with Soliris. Although there were no apparent age-related differences observed in these studies, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

## 10 OVERDOSAGE

No cases of Soliris overdose have been reported during clinical studies.

## 11 DESCRIPTION

Soliris, a complement inhibitor, is a formulation of eculizumab which is a recombinant humanized monoclonal IgG2/4<sub>κ</sub> antibody produced by murine myeloma cell culture and purified by standard bioprocess technology. Eculizumab contains human constant regions from human IgG2 sequences and human IgG4 sequences and murine complementarity-determining regions grafted onto the human framework light- and heavy-chain variable regions. Eculizumab is composed of two 448 amino acid heavy chains and two 214 amino acid light chains and has a molecular weight of approximately 148 kDa.

Soliris is a sterile, clear, colorless, preservative-free 10 mg/mL solution for intravenous infusion and is supplied in 30-mL single-use vials. The product is formulated at pH 7 and each vial contains 300 mg of eculizumab, 13.8 mg sodium phosphate monobasic, 53.4 mg sodium phosphate dibasic, 263.1 mg sodium chloride, 6.6 mg polysorbate 80 (vegetable origin) and Water for Injection, USP.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Eculizumab, the active ingredient in Soliris, is a monoclonal antibody that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9. Soliris inhibits terminal complement mediated intravascular hemolysis in PNH patients and complement-mediated thrombotic microangiopathy (TMA) in patients with aHUS.

A genetic mutation in patients with PNH leads to the generation of populations of abnormal RBCs (known as PNH cells) that are deficient in terminal complement inhibitors, rendering PNH RBCs sensitive to persistent terminal complement-mediated destruction. The destruction and loss of these PNH cells (intravascular hemolysis) results in low RBC counts (anemia), and also fatigue, difficulty in functioning, pain, dark urine, shortness of breath, and blood clots.

In aHUS, impairment in the regulation of complement activity leads to uncontrolled terminal complement activation, resulting in platelet activation, endothelial cell damage and thrombotic microangiopathy.

### 12.2 Pharmacodynamics

In the PNH placebo-controlled clinical study, Soliris when administered as recommended reduced hemolysis as shown by the reduction of serum LDH levels from  $2200 \pm 1034$  U/L (mean  $\pm$  SD) at baseline to  $700 \pm 388$  U/L by week one and maintained the effect through the end of the study at week 26 ( $327 \pm 433$  U/L). In the single arm clinical study, Soliris maintained this effect through 52 weeks [*see Clinical Studies (14)*].

### 12.3. Pharmacokinetics

A population PK analysis with a standard 1-compartmental model was conducted on the multiple dose PK data from 40 PNH patients receiving the recommended Soliris regimen [*see Dosage and Administration (2.1)*]. In this model, the clearance of Soliris for a typical PNH patient weighing 70 kg was 22 mL/hr and the volume of distribution was 7.7 L. The half-life was  $272 \pm 82$  hrs (mean  $\pm$  SD). The mean observed peak and trough serum concentrations of Soliris by week 26 were  $194 \pm 76$  mcg/mL and  $97 \pm 60$  mcg/mL, respectively.

A second population PK analysis with a standard 1 compartmental model was conducted on the multiple dose PK data from 57 aHUS patients receiving the recommended Soliris regimen in studies 1, 2 and 3. In this model, the clearance of Soliris for a typical aHUS patient weighing 70 kg was 14.6 mL/hr and the volume of distribution was 6.14 L. The elimination half-life was 291 h (approximately 12.1 days).

The clearance and half-life of eculizumab were also evaluated during plasma exchange interventions. Plasma exchange increased the clearance of eculizumab to 3660 mL/hr and reduced the half-life to 1.26 hours. Supplemental dosing is recommended when Soliris is administered to aHUS patients receiving plasma infusion or exchange [*see Recommended Dosage Regimen (2.1)*].

Dedicated studies have not been conducted to evaluate the PK of Soliris in special patient populations identified by gender, race, age (pediatric or geriatric), or the presence of renal or hepatic impairment. Pediatric and adolescent patients (less than 18 years of age) and patients with renal impairment were included in the aHUS clinical studies [*see Clinical Studies (14)*]. Population PK analysis showed age, gender, race, and renal function do not influence the PK of eculizumab.

## **13 NONCLINICAL TOXICOLOGY**

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

Long-term animal carcinogenicity studies of eculizumab have not been conducted.

Genotoxicity studies have not been conducted with eculizumab.

Effects of eculizumab upon fertility have not been studied in animals. Intravenous injections of male and female mice with a murine anti-C5 antibody at up to 4-8 times the equivalent of the clinical dose of Soliris had no adverse effects on mating or fertility.

## **14 CLINICAL STUDIES**

### **14.1 PNH**

The safety and efficacy of Soliris in PNH patients with hemolysis were assessed in a randomized, double-blind, placebo-controlled 26 week study (Study 1); PNH patients were also treated with Soliris in a single arm 52 week study (Study 2); and in a long term extension study. Patients received meningococcal vaccination prior to receipt of Soliris. In all studies, the dose of Soliris was 600 mg study drug every  $7 \pm 2$  days for 4 weeks, followed by 900 mg  $7 \pm 2$  days later, then 900 mg every  $14 \pm 2$  days for the study duration. Soliris was administered as an intravenous infusion over 25 - 45 minutes.

#### Study 1:

PNH patients with at least four transfusions in the prior 12 months, flow cytometric confirmation of at least 10% PNH cells and platelet counts of at least 100,000/microliter were randomized to either Soliris (n = 43) or placebo (n = 44). Prior to randomization, all patients underwent an initial observation period to confirm the need for RBC transfusion and to identify the hemoglobin concentration (the "set-point") which would define each patient's hemoglobin stabilization and transfusion outcomes. The hemoglobin set-point was less than or equal to 9 g/dL in patients with symptoms and was less than or equal to 7 g/dL in patients without symptoms. Endpoints related to hemolysis included the numbers of patients achieving hemoglobin stabilization, the number of RBC units transfused, fatigue, and health-related quality of life. To achieve a designation of hemoglobin stabilization, a patient had to maintain a hemoglobin concentration above the hemoglobin set-point and avoid any RBC transfusion for the entire 26 week period. Hemolysis was monitored mainly by the measurement of serum LDH levels, and the proportion of PNH

RBCs was monitored by flow cytometry. Patients receiving anticoagulants and systemic corticosteroids at baseline continued these medications.

Major baseline characteristics were balanced (see Table 7).

**Table 7: PNH Study 1 Patient Baseline Characteristics**

| Parameter  | Study 1           |                   |
|--|-------------------|-------------------|
|  | Placebo<br>N = 44 | Soliris<br>N = 43 |
| Mean age (SD)  | 38 (13)           | 42 (16)           |
| Gender - female (%)  | 29 (66)           | 23 (54)           |
| History of aplastic anemia or myelodysplastic syndrome (%)                     | 12 (27)           | 8 (19)            |
| Patients with history of thrombosis (events)                                   | 8 (11)            | 9 (16)            |
| Concomitant anticoagulants (%)   | 20 (46)           | 24 (56)           |
| Concomitant steroids/immunosuppressant treatments (%)                          | 16 (36)           | 14 (33)           |
| Packed RBC units transfused per patient in previous 12 months (median (Q1,Q3)) | 17 (14, 25)       | 18 (12, 24)       |
| Mean Hgb level (g/dL) at setpoint (SD)   | 8 (1)             | 8 (1)             |
| Pre-treatment LDH levels (median, U/L)   | 2,234             | 2,032             |
| Free hemoglobin at baseline (median, mg/dL)                                    | 46                | 41                |

Patients treated with Soliris had significantly reduced ( $p < 0.001$ ) hemolysis resulting in improvements in anemia as indicated by increased hemoglobin stabilization and reduced need for RBC transfusions compared to placebo treated patients (see Table 8). These effects were seen among patients within each of the three pre-study RBC transfusion strata (4 - 14 units; 15 - 25 units; > 25 units). After 3 weeks of Soliris treatment, patients reported less fatigue and improved health-related quality of life. Because of the study sample size and duration, the effects of Soliris on thrombotic events could not be determined.

**Table 8: PNH Study 1 Results**

|  | Placebo<br>N = 44 | Soliris<br>N = 43 |
|--|-------------------|-------------------|
| Percentage of patients with stabilized hemoglobin levels | 0                 | 49                |
| Packed RBC units transfused per patient (median)         | 10                | 0                 |
| (range)  | (2 - 21)          | (0 - 16)          |
| Transfusion avoidance (%)                                | 0                 | 51                |
| LDH levels at end of study (median, U/L)                 | 2,167             | 239               |
| Free hemoglobin at end of study (median, mg/dL)          | 62                | 5                 |

### Study 2 and Extension Study:

PNH patients with at least one transfusion in the prior 24 months and at least 30,000 platelets/microliter received Soliris over a 52-week period. Concomitant medications included anti-thrombotic agents in 63% of the patients and systemic corticosteroids in 40% of the patients. Overall, 96 of the 97 enrolled patients completed the study (one patient died following a thrombotic event). A reduction in intravascular hemolysis as measured by serum LDH levels was sustained for the treatment period and resulted in a reduced need for RBC transfusion and less fatigue. 187 Soliris-treated PNH patients were enrolled in 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 aHUS**

Three single-arm studies [(two prospective (aHUS Studies 1 and 2) and one retrospective (aHUS Study 3)] 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  $7 \pm 2$  days for 4 weeks, followed by 1200 mg  $7 \pm 2$  days later, then 1200 mg every  $14 \pm 2$  days thereafter. The dosage regimen for pediatric patients weighing less than 40 kg enrolled in aHUS Study 3 was based on body weight [*see Recommended Dosage Regimen (2.2)*]. Efficacy evaluations were based on thrombotic microangiopathy (TMA) endpoints.

Endpoints related to TMA included the following:

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

### **aHUS Resistant to PE/PI (aHUS Study 1)**

aHUS Study 1 enrolled patients who displayed signs of thrombotic microangiopathy (TMA) despite receiving at least four PE/PI treatments the week prior to screening. One patient had no PE/PI the week prior to screening because of PE/PI intolerance. In order to qualify for enrollment, patients were required to have a platelet count  $\leq 150 \times 10^9/L$ , evidence of hemolysis such as an elevation in serum LDH, and serum creatinine above

the upper limits of normal, without the need for chronic dialysis. The median patient age was 28 (range: 17 to 68 years). Patients enrolled in aHUS Study 1 had an ADAMTS-13 level above 5%. Seventy-six percent of patients had an identified complement regulatory factor mutation or auto-antibody. Table 9 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in aHUS Study 1.

**Table 9: Baseline Characteristics of Patients Enrolled in aHUS Study 1**

| Parameter   | aHUS Study 1<br>N = 17 |
|---|------------------------|
| Time from aHUS diagnosis until screening in months, median (min, max)                     | 10 (0.26, 236)         |
| Time from current clinical TMA manifestation until screening in months, median (min, max) | <1 (<1, 4)             |
| Baseline platelet count ( $\times 10^9/L$ ), median (range)                               | 118 (62, 161)          |
| Baseline LDH (U/L), median (range)  | 269 (134, 634)         |

Patients in aHUS Study 1 received Soliris for a minimum of 26 weeks. After completion of the initial 26-week treatment period, most patients continued to receive Soliris by enrolling into an extension study. In aHUS Study 1, the median duration of Soliris therapy was approximately 38 weeks (range: 2 weeks to 64 weeks).

Reduction in terminal complement activity and an increase in platelet count relative to baseline were observed after commencement of Soliris. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. In aHUS Study 1, mean platelet count increased from  $109 \pm 32 \times 10^9/L$  at baseline to  $169 \pm 72 \times 10^9/L$  by one week; this effect was maintained through 26 weeks (mean platelet count at week 26:  $210 \pm 68 \times 10^9/L$ ). Table 10 summarizes the efficacy results for aHUS Study 1.

**Table 10: Efficacy Results for aHUS Study 1 in PE/PI-Resistant aHUS**

| Efficacy Parameter  | aHUS Study 1<br>N=17 |
|---|----------------------|
| Change in platelet count from baseline through week 26 ( $\times 10^9/L$ ), least square mean (95% CI) <sup>1</sup> | 73 (40-105)          |
| Hematologic normalization <sup>2</sup> , n (%)  | 13 (76)              |
| Median Duration of hematologic normalization, weeks (range) <sup>2</sup>  | 37 (25, 62)          |
| Complete TMA response, n (%)  | 11 (65)              |
| Median Duration of complete TMA response, weeks (range) <sup>2</sup>  | 38 (25, 56)          |
| TMA event-free status, n (%)  | 15 (88)              |

| <b>Efficacy Parameter</b>  | <b>aHUS Study 1<br/>N=17</b>     |
|--|----------------------------------|
| Daily TMA intervention rate, median (range)<br>Before eculizumab<br>On eculizumab treatment  | 0.88 (0.04, 1.59)<br>0 (0, 0.31) |
| Change in eGFR (mL/min/1.73 m <sup>2</sup> ) at 26 weeks, median (range)   | +20 (-1, 98)                     |
| eGFR improvement $\geq 15$ mL/min/1.73 m <sup>2</sup> , n (%) <sup>1</sup><br>Median duration of eGFR improvement, days (range) <sup>2</sup> | 9 (53)<br>251 (70-392)           |

<sup>1</sup> Calculated at each post-dose day of measurement (excluding Days 1 to 4) through Week 26 using a repeated measurement ANOVA model.

<sup>2</sup> At data cut-off (September 8, 2010).

Renal function, as measured by median eGFR, was improved during Soliris therapy. Four of the five patients who required dialysis at study entry were able to discontinue dialysis for the duration of Soliris treatment, and one patient developed a new dialysis requirement.

In aHUS Study 1, responses to Soliris were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins.

#### **aHUS Sensitive to PE/PI (aHUS Study 2)**

aHUS Study 2 enrolled patients undergoing chronic PE/PI who generally did not display hematologic signs of ongoing thrombotic microangiopathy (TMA). All patients had received PT at least once every two weeks, but no more than three times per week, for a minimum of eight weeks prior to the first Soliris dose. Patients on chronic dialysis were permitted to enroll in aHUS Study 2. The median patient age was 28 years (range: 13 to 63 years). Patients enrolled in aHUS Study 2 had an ADAMTS-13 level above 5%. Seventy percent of patients had an identified complement regulatory factor mutation or auto-antibody. Table 11 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in aHUS Study 2.

**Table 11: Baseline Characteristics of Patients Enrolled in aHUS Study 2**

| <b>Parameter</b>  | <b>aHUS Study 2<br/>N=20</b> |
|---|------------------------------|
| Time from aHUS diagnosis until screening in months, median (min, max)                     | 48 (0.66, 286)               |
| Time from current clinical TMA manifestation until screening in months, median (min, max) | 9 (1, 45)                    |
| Baseline platelet count ( $\times 10^9/L$ ), median (range)                               | 218 (105, 421)               |
| Baseline LDH (U/L), median (range)  | 200 (151, 391)               |

Patients in aHUS Study 2 received Soliris for a minimum of 26 weeks. After completion of the initial 26-week treatment period, most patients continued to receive Soliris by enrolling into an extension study. In aHUS Study 2, the median duration of Soliris therapy was approximately 40 weeks (range: 26 to 52 weeks). Table 12 summarizes the efficacy results for aHUS Study 2.

**Table 12: Efficacy Results for aHUS Study 2 in PE/PI-Sensitive aHUS**

| Efficacy Parameter  | aHUS Study 2<br>N=20 |
|---|----------------------|
| TMA Event-free status n (%) (95% CI) <sup>1</sup>   | 16 (80) (56 - 94)    |
| Daily TMA intervention rate, median (range)   |                      |
| Before eculizumab   | 0.23 (0.05, 1.09)    |
| On eculizumab treatment   | 0                    |
| Change in platelet count from baseline through week 26 ( $\times 10^9/L$ ), least square mean (95% CI) <sup>1</sup> | 5 (-17.5 - 28)       |
| Hematologic normalization <sup>2</sup> , n (%)  | 18 (90)              |
| Median duration of hematologic normalization, weeks (range) <sup>3</sup>  | 38 (22, 52)          |
| Complete TMA response, n (%)  | 5 (25)               |
| Median duration of complete TMA response, weeks (range) <sup>3</sup>  | 32 (12, 38)          |
| Change in eGFR ( $mL/min/1.73 m^2$ ) at 26 weeks, median (range)  | +5 (-1, 20)          |
| eGFR improvement $\geq 15 mL/min/1.73 m^2$ , n (%)  | 1 (5)                |

<sup>1</sup>. Calculated at each post-dose day of measurement (excluding Days 1 to 4) through Week 26 using a repeated measurement ANOVA model.

<sup>2</sup>. In aHUS Study 2, 85% of patients had normal platelet counts and 80% of patients had normal serum LDH levels at baseline, so hematologic normalization in this population reflects maintenance of normal parameters in the absence of PE/PI.

<sup>3</sup>. At data cut-off (October 10, 2010).

In aHUS Study 2, responses to Soliris were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins. Reduction in terminal complement activity was observed in all patients after commencement of Soliris. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. Platelet counts were maintained at normal levels despite the elimination of PE/PI. The mean platelet count was  $229 \pm 78 \times 10^9/L$  at baseline, and  $233 \pm 69 \times 10^9/L$  at week 26. Renal function, as measured by median eGFR, was maintained during Soliris therapy. No patient required new dialysis with Soliris.

### **Retrospective Study in Patients with aHUS (aHUS Study 3)**

The efficacy results for the aHUS retrospective study (aHUS Study 3) were generally consistent with results of the two prospective studies. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline. Mean platelet count increased from  $171 \pm 83 \times 10^9/L$  at baseline to 233

$\pm 109 \times 10^9/L$  after one week of therapy; this effect was maintained through 26 weeks (mean platelet count at week 26:  $254 \pm 79 \times 10^9/L$ ).

A total of 19 pediatric patients (ages 2 months to 17 years) received Soliris in aHUS Study 3. The median duration of Soliris therapy was 16 weeks (range 4 to 70 weeks) for children < 2 years of age (n=5), 31 weeks (range 19 to 63 weeks) for children 2 to <12 years of age (n=10), and 38 weeks (range 1 to 69 weeks) for patients 12 to 17 years of age (n=4). Fifty three percent of pediatric patients had an identified complement regulatory factor mutation or auto-antibody.

Overall, the efficacy results for these pediatric patients appeared consistent with what was observed in patients enrolled in aHUS Studies 1 and 2 (Table 13). No pediatric patient required new dialysis during treatment with Soliris.

**Table 13: Efficacy Results in Pediatric Patients Enrolled in aHUS Study 3**

| <b>Efficacy Parameter</b>   | <b>&lt;2 yrs<br/>(n=5)</b> | <b>2 to &lt;12 yrs<br/>(n=10)</b> | <b>12 to &lt;18 yrs<br/>(n=4)</b> | <b>Total<br/>(n=19)</b> |
|---|----------------------------|-----------------------------------|-----------------------------------|-------------------------|
| Platelet count normalization, n (%) <sup>1</sup>  | 4 (80)                     | 10 (100)                          | 3 (75)                            | 17 (89)                 |
| Hematologic Normalization, n (%)  | 2 (40)                     | 5 (50)                            | 1 (25)                            | 8 (42)                  |
| Complete TMA response, n (%)  | 2 (40)                     | 5 (50)                            | 1 (25)                            | 8 (42)                  |
| Daily TMA intervention rate,<br>median (range)  |                            |                                   |                                   |                         |
| Before eculizumab   | 1 (0, 2)                   | <1 (0.07, 1.46)                   | <1 (0, 1)                         | 0.31 (0.00, 2.38)       |
| On eculizumab treatment   | <1 (0, <1)                 | 0 (0, <1)                         | 0 (0, <1)                         | 0.00 (0.00, 0.08)       |
| Patients with eGFR improvement $\geq$<br>15 mL/min/1.73 m <sup>2</sup> , n (%) <sup>2</sup> | 2 (40)                     | 6 (60)                            | 1 (25)                            | 9 (47)                  |

<sup>1</sup> Platelet count normalization was defined as a platelet count of at least  $150,000 \times 10^9/L$  on at least two consecutive measurements spanning a period of at least 4 weeks.

<sup>2</sup> Of the 9 patients who experienced an eGFR improvement of at least 15 mL/min/1.73 m<sup>2</sup>, one received dialysis throughout the study period and another received eculizumab as prophylaxis following renal allograft transplantation.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Soliris (eculizumab) is supplied as 300 mg single-use vials containing 30 mL of 10 mg/mL sterile, preservative-free Soliris solution per vial.

Soliris vials must be stored in the original carton until time of use under refrigerated conditions at 2-8° C (36-46° F) and protected from light. Do not use beyond the expiration date stamped on the carton. Refer to *Dosage and Administration* (2) for information on the stability and storage of diluted solutions of Soliris.

**DO NOT FREEZE. DO NOT SHAKE.**

NDC 25682-001-01 Single unit 300 mg carton: Contains one (1) 30 mL vial of Soliris (10 mg/mL).

## 17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (*Medication Guide*).

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

Patients should be informed that they are required to receive a meningococcal vaccination at least 2 weeks prior to receiving the first dose of Soliris, if they have not previously been vaccinated. They are required to be revaccinated according to current medical guidelines for meningococcal vaccine use while on Soliris therapy. Patients should also be informed that vaccination may not prevent meningococcal infection. Patients should be educated about any of the signs and symptoms of meningococcal infection, and strongly advised to seek immediate medical attention if these signs or symptoms occur. These signs and symptoms are as follows:

- headache with nausea or vomiting
- headache and a fever
- headache with a stiff neck or stiff back
- fever of 103° F (39.4° C) or higher
- fever and a rash
- confusion
- muscle aches with flu-like symptoms
- eyes sensitive to light

Patients should be informed 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.

Patients should also be informed that there may be an increased risk of other types of infections, particularly those due to encapsulated bacteria. Parents or caregivers of children receiving Soliris for the treatment of aHUS should be informed that their child should be vaccinated against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) according to current medical guidelines.

Patients with PNH should be informed that they may develop hemolysis due to PNH when Soliris is discontinued and that they will be monitored by their healthcare professional for at least 8 weeks following Soliris discontinuation. Patients with aHUS should be informed 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. Patients who discontinue Soliris should be instructed 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:

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US License Number 1743

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Patent No. 6,355,245 in addition to others including patents pending.