

# SOLIRIS® (ECULIZUMAB)

for the Treatment of Patients with Three Devastating or Debilitating, Rare, Complement-Mediated Disorders



## SOLIRIS® (ECULIZUMAB) OVERVIEW

The complement system is a part of the immune system that, when activated in an uncontrolled and chronic manner, can mediate debilitating and potentially life-threatening rare diseases such as paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS) and generalized myasthenia gravis (gMG).<sup>1-6</sup> Soliris is a first-in-class complement inhibitor that targets the underlying causes of these diseases by selectively and effectively inhibiting the terminal complement cascade.<sup>7</sup>

Soliris has earned some of the pharmaceutical industry's highest honors, including the 2008 Prix Galien USA Award for Best Biotechnology Product and the 2009 Prix Galien France Award in the category of Drugs for Rare Diseases.

*Please see Important Safety Information, including boxed warning for meningococcal infections, on page 3.*

## PNH – COMPLEMENT-MEDIATED HEMOLYSIS<sup>1,2</sup>

Patients with PNH have abnormal red blood cells that lack certain proteins on their surface, which normally regulate or prevent attacks by the complement system. The chronic, uncontrolled complement attack in PNH leads to hemolysis (the destruction of red blood cells)<sup>8</sup>, which in turn can result in progressive anemia, fatigue, dark urine and shortness of breath.<sup>9-11</sup> The most

devastating consequence of chronic hemolysis is thrombosis (the formation of blood clots), which can damage vital organs and cause premature death.<sup>12</sup>

Soliris is the first and only approved treatment for patients with PNH. By inhibiting the terminal complement cascade, it reduces hemolysis in these patients (as measured by reduced lactate dehydrogenase [LDH] levels), which can result in fewer thrombotic events, reduced need for transfusions, and improvements in fatigue and health-related quality of life.<sup>7,12-14</sup> Soliris is approved in nearly 50 countries worldwide for the treatment of patients with PNH, including the United States (U.S.), the European Union (EU) and Japan.

## aHUS – COMPLEMENT-MEDIATED INFLAMMATION AND CLOTTING IN SMALL BLOOD VESSELS<sup>3,4,15,16</sup>

In patients with aHUS, uncontrolled complement activation due to the lack of certain regulatory proteins or the presence of certain auto-antibodies causes thrombotic microangiopathy (TMA)—the formation of blood clots and inflammation in small blood vessels throughout the body.<sup>3,4,15,16</sup> This can result in potentially irreversible damage to the kidneys and other vital organs, sudden or progressive kidney failure (requiring dialysis or transplant) and premature death. TMA can also lead to reduced platelet count (thrombocytopenia) and hemolysis (the destruction of red blood cells).<sup>16-18</sup>

Soliris is the first and only approved treatment for patients with aHUS.<sup>7</sup> By inhibiting the terminal complement cascade, it reduces TMA in patients with aHUS (as measured through hematologic markers of complement-mediated TMA, including platelet counts and LDH levels) and can improve renal function (as measured by estimated glomerular filtration rate [eGFR]).<sup>5,7,19-21</sup> Soliris is

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approved in more than 40 countries for the treatment of aHUS, including the U.S., the EU and Japan.

### COMPLEMENT-MEDIATED gMG – A DEBILITATING NEUROMUSCULAR DISORDER<sup>6</sup>

Patients with gMG can have difficulties seeing, walking, talking, chewing, swallowing and breathing normally due to profound muscle weakness. Disease exacerbations and crises may require hospitalization and intensive care and may be life-threatening.<sup>22-24</sup> An estimated 5-10% of patients with MG have significant unresolved disease symptoms despite existing therapies and also have auto-antibodies against the acetylcholine receptor (AChR) that plays an important role in the communication between nerves and muscles.<sup>25-28</sup> Chronic complement activation by anti-AChR antibodies is an important underlying cause of the disease in these patients.<sup>6</sup>

Soliris is the first and only complement inhibitor approved in the U.S. for adult patients with gMG who are anti-AChR antibody-positive.<sup>7</sup> By inhibiting the terminal complement cascade, it improves muscle strength and the ability to carry out activities of daily living (as measured by changes in MG-Activities of Daily Living [MG-ADL] and Quantitative MG [QMG], which are MG-specific assessment scales), signs and symptoms of MG and MG-specific quality of life.<sup>7,29,30</sup> Soliris is approved in the EU as a treatment for refractory gMG in adults who are anti-AChR antibody-positive.<sup>31</sup> In addition, Alexion has submitted a new drug application for Soliris as a treatment for patients with anti-AChR antibody-positive refractory gMG in Japan.

### CLINICAL STUDIES

The efficacy and safety of Soliris for the treatment of patients with PNH who were experiencing hemolysis were demonstrated in three multi-national Phase 3 clinical studies:<sup>7,12-14,32</sup>

- The randomized, double-blind, multi-center placebo-controlled 26-week TRIUMPH Study, which comprised 87 transfusion-dependent patients with PNH receiving Soliris (43 patients) or placebo (44 patients).
- The single-arm SHEPHERD Study comprising 97 patients with PNH treated with Soliris for 52 weeks.
- A long-term extension study that included 187 patients with PNH initially enrolled in one of three parent trials (195 patients) who continued to receive Soliris for a range of 10 to 54 months.

The majority of patients (63%) received concomitant anticoagulant therapy. The effect of anticoagulant withdrawal during Soliris treatment has not been studied.

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.<sup>7</sup>

The efficacy and safety of Soliris for the treatment of patients with aHUS were demonstrated in four multinational prospective Phase 2 open-label clinical studies in pediatric, adolescent and adult patients with aHUS (100 patients), and a fifth retrospective study in children, adolescents and adults with aHUS (30 patients).<sup>5,7,19-21</sup>

The most frequently reported adverse reactions in aHUS single arm prospective trials ( $\geq 20\%$ ) are: headache, diarrhea, hypertension, upper respiratory infection, abdominal pain, vomiting, nasopharyngitis, anemia, cough, peripheral edema, nausea, urinary tract infections and pyrexia.<sup>7</sup>

The efficacy and safety of Soliris for the treatment of adult patients with anti-AChR antibody-positive gMG was established in the Phase 3, placebo-controlled multinational clinical REGAIN study (125 patients) and is evaluated further in its ongoing open-label extension study (117 patients). Treatment effects were measured across four MG-specific assessment scales (MG-ADL, QMG, MG Composite [MGC] and MG Quality of Life 15 [MG-QoL 15]). Enrolled patients had previously failed treatment with two or more immunosuppressive therapies (IST) (for at least one year), or failed at least one IST and required chronic plasmapheresis or plasma exchange (PE) or intravenous immunoglobulin (IVIg) to control symptoms.<sup>7,29,30</sup>

The most frequently reported adverse reaction in the gMG placebo-controlled clinical trial ( $\geq 10\%$ ) is: musculoskeletal pain.<sup>7</sup>

### INDICATIONS AND USAGE

#### PNH

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

#### 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).

#### Anti-AChR antibody-positive gMG

Soliris is indicated as a treatment for adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody-positive.

## IMPORTANT SAFETY INFORMATION

### WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

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

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.
- Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of Soliris, unless the risks of delaying Soliris therapy outweigh the risk of developing a meningococcal infection.
- 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](http://www.solirisrems.com).

## CONTRAINDICATIONS

Soliris is contraindicated in:

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

## WARNINGS AND PRECAUTIONS

### Other Infections

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

### Monitoring Disease Manifestations After Soliris Discontinuation

#### Treatment Discontinuation for PNH

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

#### Treatment Discontinuation for aHUS

After discontinuing Soliris, monitor patients with aHUS for signs and symptoms of thrombotic microangiopathy (TMA) complications for at least 12 weeks. In aHUS clinical trials, 18 patients (5 in the prospective studies) discontinued Soliris

treatment. TMA complications occurred following a missed dose in 5 patients, and Soliris was reinitiated in 4 of these 5 patients.

Clinical signs and symptoms of TMA include changes in mental status, seizures, angina, dyspnea, or thrombosis. In addition, the following changes in laboratory parameters may identify a TMA complication: occurrence of two, or repeated measurement of any one of the following: a decrease in platelet count by 25% or more compared to baseline or the peak platelet count during Soliris treatment; an increase in serum creatinine by 25% or more compared to baseline or nadir during Soliris treatment; or, an increase in serum LDH by 25% or more over baseline or nadir during Soliris treatment.

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

### Thrombosis Prevention and Management

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

### Infusion Reactions

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.

**Please see full prescribing information for Soliris, including boxed WARNING regarding serious meningococcal infection.**

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## References

1. Hill A, Richards SJ, Hillmen P. Recent developments in the understanding and management of paroxysmal nocturnal haemoglobinuria. *Br J Haematol*. 2007 May;137(3):181-92.
2. Hillmen P, Lewis SM, Bessler M, Luzzatto L, Dacie JV. Natural history of paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 1995 Nov 9;333(19):1253-8.
3. Laurence J. Atypical hemolytic uremic syndrome (aHUS): making the diagnosis. *Clin Adv Hematol Oncol*. 2012;10(suppl 17):1-12.
4. Noris M, Mescia F, Remuzzi G. STEC-HUS, atypical HUS and TTP are all diseases of complement activation. *Nat Rev Nephrol*. 2012;8:622-633.
5. Legendre C. Terminal Complement Inhibitor Eculizumab in aHUS. *N Engl J Med*. 2013;368: 2169-81.
6. Conti-Fine, et al. Myasthenia gravis: past, present, and future. *J Clin Invest*. 2006; 116:2843-2354.
7. Soliris [package insert]. New Haven, CT: Alexion Pharmaceuticals Inc; 2017
8. Rosse W. Paroxysmal Nocturnal Hemoglobinuria. Hoffman: Hematology: Basic Principles and Practice. 3rd ed. Churchill Livingstone, Inc.; 2000: 331-342.
9. Nishimura J, Kanakura Y, Ware RE, Shichishima T, Nakakuma H, Ninomiya H, et al. Clinical course and flow cytometric analysis of paroxysmal nocturnal hemoglobinuria in the United States and Japan. *Medicine (Baltimore)* 2004 May;83(3):193-207.
10. Weitz I, Meyers G, Lamy T, et al. Cross-sectional validation study of patient-reported outcomes in patients with paroxysmal nocturnal haemoglobinuria. *Intern Med J*. 2013;43:298-307.
11. Parker C, Omine M, Richards S, Nishimura J, Bessler M, Ware R, et al. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. *Blood*. 2005 Dec 1;106(12):3699-709.
12. Hillmen P, Muus P, Duhren U, Risitano AM, Schubert J, Luzzatto L, et al. Effect of the complement inhibitor eculizumab on thromboembolism in patients with paroxysmal nocturnal hemoglobinuria. *Blood*. 2007 Dec 1;110(12):4123-8.
13. Hillmen P, Young NS, Schubert J, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 2006;335:1233-1243.
14. Brodsky RA, Young NS, Antonioli E et al. Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria. *Blood*. 2008 Feb 15;111(4):1840-7. Epub 2007 Nov 30.
15. Campistol JM, Arias M, Ariceta G, et al. An update for atypical haemolytic uraemic syndrome: diagnosis and treatment. *Nefrologia*. 2013 Jan 18;33(1):27-45.
16. Sellier-Leclerc A-L, Frémeaux-Bacchi V, Dragon-Durey MA, et al; French Society of Pediatric Nephrology. Differential impact of complement mutations on clinical characteristics in atypical hemolytic uremic syndrome. *J Am Soc Nephrol*. 2007;18:2392-2400.
17. Caprioli J, Noris M, Briochi S, et al; for the International Registry of Recurrent and Familial HUS/TTP. Genetics of HUS: the impact of MCP, CFH, and IF mutations on clinical presentation, response to treatment, and outcome. *Blood*. 2006;108:1267-1279.
18. Hirt-Minkowski P, Dickenmann M, Schifferli JA. Atypical hemolytic uremic syndrome: update on the complement system and what is new. *Nephron Clin Pract*. 2010;114:c219-c235.
19. Licht C, Greenbaum LA, Muus P et al. Efficacy and safety of eculizumab in atypical hemolytic uremic syndrome from 2-year extensions of phase 2 studies. *Kidney Int*. 2015;87:1061-1073.
20. Greenbaum LA, Fila M, Ardissio G, et al. Eculizumab is a safe and effective treatment in pediatric patients with atypical hemolytic uremic syndrome. *Kidney Int*. 2016;89:701-711.
21. Fakhouri F, Hourmant M, Campistol J, et al. Terminal Complement Inhibitor Eculizumab in Adult Patients With Atypical Hemolytic Uremic Syndrome: A Single-Arm, Open-Label Trial. *Am J Kidney Dis*. 2016;68(1):84-93
22. Howard JF, Barohn RJ, Cutter GR, et al. A randomized, double-blind, placebo-controlled phase II study of eculizumab in patients with refractory generalized myasthenia gravis. *Muscle Nerve*. 2013;48(1):76-84.
23. National Institute of Neurological Disorders and Stroke. Myasthenia Gravis Fact Sheet. Last modified May 10, 2016. [http://www.ninds.nih.gov/disorders/myasthenia\\_gravis/detail\\_myasthenia\\_gravis.htm](http://www.ninds.nih.gov/disorders/myasthenia_gravis/detail_myasthenia_gravis.htm).
24. Sathasivam S. Diagnosis and management of myasthenia gravis. *Progress in Neurology and Psychiatry*. January/February 2014.
25. Silvestri N, Wolfe G. Treatment-refractory myasthenia gravis. *J Clin Neuromuscul Dis*. 2014;15(4):167-178.
26. Howard J. Myasthenia Gravis - A summary. Myasthenia Gravis Foundation of America. <http://www.myasthenia.org/HealthProfessionals/ClinicalOverviewofMG.aspx>. Accessed October 17, 2017
27. Grob D, Brunner N, Namba T, Pagala M. Lifetime course of myasthenia gravis. *Muscle Nerve*. 2008 Feb;37(2):141-9.
28. Suh J, Goldstein JM, Nowak RJ. Clinical Characteristics of Refractory Myasthenia Gravis Patients. *Yale J Biol Med*. 2013;86(2):255-260
29. Howard JF. REGAIN: A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Evaluate the Safety and Efficacy of Eculizumab in Subjects With Refractory Generalized Myasthenia Gravis (gMG). Presented at the 14th International Congress on Neuromuscular Diseases (ICNMD), Toronto, July 7, 2016.
30. Howard JF, Wang JJ, O'Brien F, Mantegazza R and the REGAIN study group. Efficacy of eculizumab is maintained beyond 26 weeks in patients with AChR+ refractory generalized myasthenia gravis (gMG). Poster (abstract 211), annual meeting of the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM), September 14, 2017.
31. Soliris® Summary of Product Characteristics, European Medicines Agency, August 2017
32. Hillmen P, Muus P, Röth A, Elebute MO, Risitano AM, Schrezenmeier H. Longterm safety and efficacy of sustained eculizumab treatment in patients with paroxysmal nocturnal haemoglobinuria. *Br J Haematol*. 2013;162:62-73.