

## Drug Class Update and Drug Evaluation: Monoclonal C5 Inhibitors

**Date of Review:** April 2021

**Generic Name:**

Ecuzumab  
Ravuzumab-cwvz

**Dates of Literature Search:** 01/01/1996-01/20/2021

**Brand Name (Manufacturer):**

Soliris® (Alexion Pharmaceuticals)  
Ultomiris® (Alexion Pharmaceuticals)

**Dossier Received:** yes

**Current Status of PDL Class:**

See **Appendix 1**.

**Purpose for Class Update:**

To define place in therapy for 2 immunosuppressive agents, ecuzumab and ravuzumab. Ecuzumab is FDA-approved for 4 indications including: 1) reducing hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH), 2) inhibiting complement-mediated thrombotic microangiopathy (TMA) in patients with atypical hemolytic-uremic syndrome (aHUS), 3) managing generalized myasthenia gravis (MG) and 4) treatment of adults with neuromyelitis optica spectrum disorder (NMOSD). Management of NMOSD is reviewed in a separate Pharmacy & Therapeutics Committee review. Ravuzumab is FDA-approved for treatment of PNH and aHUS.

**Research Questions:**

1. What is the effectiveness of ecuzumab in reducing hemolysis in patients with PNH, inhibiting complement-mediated thrombotic microangiopathy in patients with aHUS, and managing generalized MG?
2. What are the harms of ecuzumab in adults with PNH, aHUS and MG?
3. What is the efficacy of ravuzumab in reducing hemolysis in patients with PNH and inhibiting complement-mediated thrombotic microangiopathy in patients with aHUS?
4. What are the harms of ravuzumab in adults with PNH and aHUS?
5. Is there comparative evidence that ecuzumab and ravuzumab differ in efficacy or harms for management of PNH and aHUS?
6. Are there certain sub-populations (based on age, gender, ethnicity, comorbidities, disease duration or severity) in which ecuzumab or ravuzumab may be beneficial or cause more harm?

## Conclusions:

### Eculizumab

- The efficacy and safety of eculizumab in adults with PNH was demonstrated in 2 multinational, phase 3 trials. In the double-blind Transfusion Reduction Efficacy and Safety Clinical Investigation (TRIUMPH), patients with severe PNH disease (n=87) were randomized to eculizumab or placebo and evaluated over 26 weeks.<sup>1</sup> The open-label, single-arm, 52 week Safety and Efficacy of the Terminal Complement Inhibitor Eculizumab in Patients with Paroxysmal Nocturnal Hemoglobinuria (SHEPHERD) trial evaluated eculizumab in a broader PNH patient population (e.g., patients with thrombocytopenia and mild anemia; n=97).<sup>2</sup>
- Intravascular hemolysis with moderate to severe anemia, an elevated reticulocyte count, and up to a 10-fold increase in lactate dehydrogenase (LDH) is common in classic PNH.<sup>3</sup> The co-primary endpoints in the TRIUMPH trial were the stabilization of hemoglobin levels and the number of units of packed red cells transfused.<sup>1</sup> Low-quality evidence showed stabilization of hemoglobin levels and the requirement for packed red cell transfusions were improved significantly more with eculizumab than with placebo after 26 weeks of treatment.<sup>1</sup> Forty-nine percent of all patients in the eculizumab group were transfusion independent compared with 0% of patients in the placebo group (p<0.001).<sup>1</sup> In the SHEPHERD trial, eculizumab significantly reduced requirements for packed red cell transfusions throughout the study.<sup>2</sup> During 52 weeks of eculizumab therapy, the median number of units transfused per patient was 0 compared with 8 units in the year prior to treatment (p<0.001; low-quality evidence).<sup>2</sup>
- In the TRIUMPH trial, hemolysis was also significantly reduced with eculizumab compared with placebo, as determined by lower mean levels of LDH in the eculizumab treatment group (low-quality evidence).<sup>1</sup> The median area under the concentration-time curve (AUC) for LDH was 86% lower with eculizumab than with placebo (58,587 vs. 411,822 U/L per day respectively; p < 0.001; low-quality evidence).<sup>1</sup> In the SHEPHERD trial, hemolysis was significantly improved from baseline with eculizumab treatment, as demonstrated by the reduction in LDH AUC (median change -632,264 IU/L per day; p<0.001; low quality evidence) after 52 weeks of treatment.<sup>2</sup> Mean LDH was significantly reduced by 87%, from 2201 IU/L at baseline to 297 IU/L at week 52 (p<0.001; low quality evidence).<sup>2</sup>
- The randomized, placebo-controlled, double-blind, multicenter, phase 3 REGAIN study evaluated the safety and efficacy of eculizumab in adults with MG.<sup>4</sup> The primary efficacy endpoint was the change from baseline to week 26 in Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score according to a prespecified worst-rank ANCOVA strategy.<sup>4</sup> The primary analysis showed no significant difference between eculizumab and placebo (least-squares mean rank 56.6 vs. 68.3; rank-based treatment difference -11.7; 95% CI -24.3 to 0.96; p=0.0698; moderate-quality evidence).<sup>4</sup>
- Two, single-arm, multinational, 26-week, phase 2 trials evaluated intravenous eculizumab inhibition of complement-mediated thrombotic microangiopathy (TMA) in patients aged 12 years and older with aHUS.<sup>5</sup> Complete TMA response was defined as hematologic normalization plus improvement in renal function (25% reduction from baseline in serum creatinine in two consecutive measurements for four or more weeks).<sup>5</sup> Trial C08-002 included patients with progressive TMA who were refractory to plasma exchange or infusion while Trial C08-003 included patients with chronic dependence on plasma exchange or infusion.<sup>5</sup> At week 26, 65% and 25% of patients demonstrated complete TMA response in both trials (low-quality evidence).<sup>5</sup> At 26 weeks, the platelet count was significantly increased from baseline in patients with progressing thrombotic microangiopathy despite plasma exchange/infusion, and thrombotic microangiopathic event-free status was achieved in 80% of patients with a long disease duration and chronic kidney disease who received long-term plasma exchange/infusion (low-quality evidence).<sup>5</sup>
- The most serious risk of terminal complement blockade is life-threatening *Neisseria* infections (roughly 0.5%/year or 5% after 10 years).<sup>3</sup> Thus, all patients treated with eculizumab should be vaccinated against *Neisseria* with the use of locally approved vaccines.<sup>3</sup> In severe PNH cases, especially those with concomitant thrombosis, administration of eculizumab and vaccination can be performed on the same day. In such cases, 2 weeks of prophylactic therapy with ciprofloxacin is recommended.<sup>6</sup>
- The most common adverse events associated with eculizumab in the 26-week TRIUMPH<sup>1</sup> and 52-week SHEPHERD<sup>2</sup> studies in patients with PNH were headache (44%<sup>1</sup> and 53%<sup>2</sup>) and nasopharyngitis (23%<sup>1</sup> and 32%<sup>2</sup>). The majority of adverse events in both studies were mild to moderate in intensity.

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## Ravulizumab

- In December 2018, the US Food and Drug Administration approved ravulizumab for the treatment of PNH, based on the results of two phase 3 non-inferiority clinical trials. In the first trial, ALXN1210-PNH-301, ravulizumab was administered to C5 inhibitor-naïve PNH patients and compared to eculizumab,<sup>7</sup> and in the second trial, ALXN1210-PNH-302, ravulizumab and eculizumab were evaluated for noninferiority in stable PNH patients previously treated with eculizumab.<sup>8</sup>
- In C5 inhibitor-naïve patients, transfusion avoidance in ravulizumab (n = 125) and eculizumab (n = 121) treatment arms was achieved in 73.6% and 66.1% of patients, respectively, with a between-group difference of 6.8% (95% CI – 4.66 to +18.14; p<0.0001 for noninferiority; low-quality evidence).<sup>7</sup> The lower bound of the 95% CI was greater than the protocol-specified noninferiority margin of –20%.<sup>7</sup> The noninferiority margin for the coprimary endpoint of LDH normalization was based on a previous randomized, placebo-controlled study of eculizumab<sup>1</sup> and adjusted to the observed baseline LDH normalization of recent phase 1b and 2 studies, calculated with a weighted average of the proportions of LDH normalization from day 29 to day 183.<sup>7</sup> LDH normalization was achieved in 53.6% versus 49.4% of patients (adjusted odds ratio 1.19; 95% CI 0.80–1.77; p < 0.0001 for noninferiority; low-quality evidence).<sup>7</sup> The lower bound of the 95% CI was greater than the protocol-specified noninferiority margin of 0.39.<sup>7</sup>
- In stable patients previously treated with eculizumab, the mean percentage change in LDH in ravulizumab (n = 97) and eculizumab (n = 98) treatment arms was –0.82% versus +8.39% [treatment difference of 9.21% (95% CI – 0.42 to 18.84); p<0.0006 for inferiority; low-quality evidence].<sup>8</sup> The lower bound of the 95% CI for the difference was –0.42%, which exceeded the protocol-specified noninferiority margin of –15%, indicating that ravulizumab is noninferior to eculizumab.<sup>8</sup>
- A prospective, open-label, phase 3 trial evaluated the efficacy and safety of ravulizumab in adults with aHUS.<sup>9</sup> In this global, multicenter, single arm study, patients received intravenous ravulizumab as a weight-based loading dose on day 1, followed by weight-based maintenance doses on day 15 and every 8 weeks thereafter.<sup>9</sup> Low-quality evidence showed after 26 weeks of treatment with ravulizumab, complete thrombotic microangiopathy response (TMA; primary efficacy endpoint) was seen in 53.6% of complement-inhibitor naïve adult patients with aHUS (n = 56).<sup>9</sup>
- Common adverse effects associated with ravulizumab administration may include upper respiratory tract infection and headache.<sup>10</sup>
- In the United States, ravulizumab and eculizumab are available only through restricted Risk Evaluation and Mitigation Strategy (REMS) programs.<sup>6,10</sup> Ravulizumab and eculizumab prescribing information contains a black box warning due to an increased risk of life-threatening and fatal meningococcal infections.<sup>6,10</sup>

## Monoclonal C5 Inhibitors

- There is insufficient evidence to evaluate the use of eculizumab and ravulizumab in the treatment specific subpopulations based on age, gender, ethnicity, comorbidities, disease duration or severity.

## Recommendations:

- Create a new class of drugs on the PDL entitled “Biologics for Rare Diseases” and include eculizumab and ravulizumab in this new class.
- Implement clinical prior authorization criteria for eculizumab and ravulizumab to ensure appropriate utilization in FDA-approved indications funded by Oregon Health Plan (**Appendix 4**).
- After review of costs in executive session, make eculizumab non-preferred and ravulizumab preferred.

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**Background:*****Paroxysmal Nocturnal Hemoglobinuria***

PNH is a rare disease that presents with a variety of symptoms, the most prevalent of which are hemolytic anemia, hemoglobinuria, fatigue and shortness of breath.<sup>11</sup> Other findings associated with PNH include thrombosis, renal insufficiency, and in the later course of the disease, bone marrow failure.<sup>11</sup> The rarity of the disease and nonspecific symptoms can result in significant delays in diagnosis.<sup>11</sup> The condition is genetic, with the mutations occurring on the X-linked gene.<sup>11</sup> This mutation of the X-linked gene phosphatidylinositol glycan class A (PIGA) produces a deficiency in the glycosylphosphatidylinositol (GPI) protein, which is responsible for anchoring other protein moieties to the surface of erythrocytes.<sup>11</sup> Proteins responsible for the regulation of complement activity, specifically CD55 and CD59, are thereby prevented from attaching to PNH affected cells.<sup>11</sup> This leads to activation of C3, C5, and the terminal pathway of complement culminating in the formation of the membrane attack complex (MAC).<sup>3</sup> Under normal conditions, formation of the MAC is under the regulation of CD59.<sup>3</sup> The absence of CD59 on PNH erythrocytes leads to uncontrolled formation of the MAC resulting in complement-mediated intravascular hemolysis.<sup>3</sup> This chronic state of hemolysis can be exacerbated if the complement system is activated by stress due to surgery, trauma, or other triggers for inflammation.<sup>11</sup>

Anemia in PNH is often multifactorial and may result from a combination of hemolysis and bone marrow failure.<sup>3</sup> Intravascular hemolysis with moderate to severe anemia, an elevated reticulocyte count, and up to a 10-fold increase in lactate dehydrogenase (LDH) is common in classic PNH.<sup>3</sup> Patients with classic PNH often have a high percentage of PNH granulocytes (greater than 50%). PNH in the context of other primary marrow disorders usually refers to acquired aplastic anemia.<sup>3</sup> Thrombosis leads to severe morbidity and is the most common cause of mortality in PNH.<sup>3</sup> Thrombosis in PNH may occur at any site; however, venous thrombosis is more common than arterial.<sup>3</sup> Deep venous thrombosis, pulmonary emboli, and dermal thrombosis are also relatively common.<sup>3</sup> Abdominal pain, esophageal spasm, dysphagia, and erectile dysfunction are common symptoms associated with classic PNH and are a direct consequence of intravascular hemolysis and the release of free hemoglobin.<sup>3</sup> Free hemoglobin is normally cleared by haptoglobin, CD163, and hemopexin.<sup>3</sup> These clearing mechanisms are overwhelmed in PNH and lead to accumulation of high levels of free hemoglobin in the plasma and consequently, depletion of nitric oxide.<sup>3</sup> Renal tubular damage is caused by microvascular thrombosis and accumulation of iron deposits. Raised pulmonary pressures and reduced right ventricular function caused by subclinical microthrombi and hemolysis-associated nitric oxide scavenging contribute to symptoms of fatigue and dyspnea.<sup>3</sup>

A classification scheme, proposed by the International PNH Interest Group, includes 3 main categories of PNH: (1) classic PNH, which includes hemolytic and thrombotic patients; (2) PNH in the context of other primary bone marrow disorders, such as aplastic anemia or myelodysplastic syndrome; and (3) subclinical PNH, in which patients have small PNH clones but no clinical or laboratory evidence of hemolysis or thrombosis.<sup>12</sup> This classification scheme has resulted in some confusion because varying degrees of bone marrow failure underlie virtually all cases of PNH; thus, the distinction between 3 categories may be difficult in some cases.<sup>3</sup>

PNH is rare, with occurrence estimated as high as 15.9 individuals per million worldwide.<sup>13</sup> Some authors indicate that this number is probably low as the disease remains undiagnosed in individuals with limited symptomatology, or with comorbid conditions that obscure the PNH diagnosis.<sup>14</sup> Typically most patients are diagnosed at 30 years to 40 years of age.<sup>11</sup> Children can be affected by PNH as well, but it is uncommon.<sup>11</sup> According to an analysis of 1610 patients registered in the International PNH Registry in 2012, the median age of all registered patients was 42 years, with the disease duration of 4.6 years.<sup>15</sup> The age range of patients in the registry was 3 to 99 years.<sup>15</sup> While the occurrence of PNH has no apparent ethnic or geographic distribution, there is an increased risk of thrombosis in the United States and Europe.<sup>11</sup> About 30 to 40% of PNH cases are reported in the United States (U.S.) and Europe, whereas less than 10% of PNH cases are reported from Asia.<sup>11</sup> Consequently, the incidence of thromboembolism due to PNH is higher in the U.S. and Europe compared to Japan.<sup>16</sup> Patients affected by PNH in the U.S. demonstrate differences in complications according to ethnic groups. African-Americans with PNH have a 73% rate of thromboembolism and Latin

Americans, about 50%.<sup>11</sup> White race and Asian Americans have a 36% rate of thromboembolism complications.<sup>11</sup> Bone marrow failure also varies with ethnicity or geography.<sup>11</sup> It is more common in residents of Asia, the Pacific Islands, and Latin America.<sup>11</sup> The reasons for these variations are not clear.<sup>11</sup>

In the past, PNH treatment was mostly supportive.<sup>11</sup> Patients were given a blood transfusion and iron supplementation for recurrent hemolysis and anemia and anti-thrombosis prophylaxis was initiated to prevent thrombosis.<sup>11</sup> For severe, life-threatening bone marrow complications, an allogeneic bone marrow transplant was offered.<sup>11</sup> The mainstay of current therapy for PNH includes drugs to block alternative complement pathways such as eculizumab or ravulizumab, and allogeneic hematopoietic stem cell transplantation.<sup>11</sup> There are many other anti-C5 monoclonal antibodies therapies under investigation.<sup>11</sup> Other novel therapy development projects are focusing on targets upstream in the complement pathway, such as C1 inhibitors, C3 inhibitors, and Factor D inhibition therapies.<sup>11</sup>

### ***Atypical Hemolytic-Uremic Syndrome***

Atypical HUS is a rare variant of thrombotic microangiopathy that is caused by abnormalities of the alternative complement pathway resulting in endothelial cell dysfunction and formation of microvascular thrombi that can result in serious thrombotic events such as stroke.<sup>17</sup> Atypical HUS is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and renal impairment.<sup>17</sup> Atypical HUS earned its name because it is not caused by either of the common etiological factors for typical HUS (Shiga toxin produced by *E. coli O157:H7* or *S. dysenteriae*).<sup>17</sup> When patients are negative for Shiga toxin, other etiologies such as genetic and sporadic causes must be further investigated.<sup>17</sup> The condition predominantly affects the kidneys but has the potential to cause multi-organ system dysfunction.<sup>17</sup> This uncommon disorder is caused by a genetic abnormality in the complement alternative pathway resulting in over-activation of the complement system and formation of microvascular thrombi.<sup>17</sup> Abnormalities of the complement pathway may be in the form of mutations in key complement genes or autoantibodies against specific complement factors.<sup>17</sup> Genetic or acquired dysregulation of the complement alternative pathway is detected in 40–60% of patients with aHUS suggesting a genetic predisposition.<sup>17</sup> This dysregulation is caused by mutations in genes that encode complement regulatory proteins, Factor H (FH), Factor I (FI), membrane cofactor protein, complement 3 (C3), Factor B (FB) or thrombomodulin, or presence of anti-FH antibody resulting in activation of the complement system.<sup>17</sup>

Complement is part of the innate immune response, helping host cells clear pathogens via three distinct pathways: classic, lectin, and alternative.<sup>17</sup> These pathways ultimately converge to create C3 convertase, a complex that initiates MAC (C5-9) formation to destroy target cells via attachment and lysis.<sup>17</sup> Over-activation of the alternative complement pathway in aHUS occurs due to either the production of FH autoantibodies or due to genetic complement protein mutations such as FH, FI, FB, C3, and thrombomodulin.<sup>17</sup> The complement abnormality that is associated with aHUS is very rare with only roughly 1000 reported cases.<sup>17</sup> The incidence of aHUS is estimated to be 0.23–0.42 cases per million; children constitute 0.10–0.11 cases per million.<sup>17</sup> The disease has been triggered by pregnancy, viral illness, and sepsis among other causes; approximately 30% of aHUS results from unknown mechanisms.<sup>17</sup> Regardless of the cause, aHUS is a rare disorder with poor clinical outcomes, and higher morbidity and mortality than infection-associated typical HUS.<sup>17</sup> Atypical HUS has a mortality rate of 25% and about 50% of patients may develop irreversible end stage renal disease (ESRD), requiring renal transplant or chronic dialysis.<sup>17</sup>

Atypical HUS can present at any age and is of acute onset in 20% of cases.<sup>17</sup> The clinical presentation depends upon the extent of microvascular injury and thrombosis, as well as ischemic injury to various organ systems.<sup>17</sup> Patients with aHUS present with hemolytic anemia (hemoglobin <10 g/dL), thrombocytopenia (platelets <150,000/mm<sup>3</sup>), and impaired renal function. Renal impairment is frequent; most common manifestations are proteinuria, hematuria, hypertension, and azotemia.<sup>17</sup> While proteinuria is typically mild, nephrotic range proteinuria may occur.<sup>17</sup> A majority of patients require chronic renal replacement therapy.<sup>17</sup> Hypertension is often moderate to severe, due to vascular disease and volume expansion.<sup>17</sup> Atypical HUS presents as a systemic disease, and extra-renal features are seen in 20% and a catastrophic presentation with multi-organ involvement in 5% of patients.<sup>17</sup>

Therapy of aHUS is supportive, with attention to management of acute kidney injury and systemic complications.<sup>17</sup> The use of packed red blood cells is necessary in patients with severe anemia. Platelet transfusions are rarely required, except in counts less than 10,000/mm<sup>3</sup>, or thrombocytopenia associated with active bleeding or in patients undergoing invasive procedures.<sup>17</sup> Fluid and electrolyte management is important to maintain intravascular volume status and combat the consequences of acute kidney injury and multisystem organ failure.<sup>17</sup> Electrolyte disturbances should be promptly corrected and nephrotoxic medications avoided.<sup>17</sup> Hypertension should be managed with appropriate agents.<sup>17</sup> Renal replacement therapy is required in patients with uremia, fluid overload, or electrolyte abnormalities.<sup>17</sup> No adequate, well-controlled trials have been conducted to establish the efficacy of plasma therapy in aHUS.<sup>17</sup> By preventing MAC formation, eculizumab and ravulizumab inhibit the mechanism by which aHUS causes pathology, making these novel drugs promising treatments for aHUS patients.<sup>17</sup>

### ***Myasthenia Gravis***

Myasthenia gravis is an autoimmune disease in which antibodies bind to acetylcholine receptors or functionally related molecules in the postsynaptic membrane at the neuromuscular junction.<sup>18</sup> Autoantibodies may be produced against 1) the skeletal muscle acetylcholine receptor (AChR); 2) muscle-specific kinase, a receptor tyrosine kinase critical for the maintenance of neuromuscular synapses; 3) low-density lipoprotein receptor-related protein 4, an important molecular binding partner for muscle-specific kinase; and 4) other muscle endplate proteins.<sup>19</sup> The antibodies induce weakness of skeletal muscles, which result in impaired speech, difficulty swallowing or chewing, shortness of breath, drooping of one or both eyelids, blurred vision and weakness in limbs.<sup>18</sup> In the most common type of MG, autoantibodies are produced that target the skeletal muscle AChR, reducing the number of functional AChRs, and causing morphological damage to the endplate membrane, resulting in the clinical phenotype of fatigable muscle weakness.<sup>19</sup> In AChR antibody-positive MG, the production of autoantibodies by pathogenic B cells is T cell-dependent.<sup>19</sup> Although anti-AChR antibodies directly contribute to the degradation of AChR at the neuromuscular junction, autoreactive T cells provide help to B cells that synthesize anti-AChR antibodies.<sup>19</sup> The situation with AChR-associated MG becomes more complicated as there are clinical and immunological differences in patients with thymic abnormalities (thymic hyperplasia vs thymoma) versus no thymic pathology.<sup>19</sup> Approximately 70% of patients with MG with anti-AChR antibodies have thymic follicular hyperplasia, approximately 10% have thymomas, and the remainder have a histologically normal or atrophic thymus gland.<sup>19</sup> The alterations of the immune system that occur with thymic hyperplasia versus thymoma are quite distinct.<sup>19</sup> In patients with thymic hyperplasia, there is evidence that the thymus is the primary site of immune sensitization to the AChR and may play a role in perpetuating the disease.<sup>19</sup> Thymic follicular hyperplasia usually occurs in early-onset MG and is characterized by the development of lymphoid germinal centers (GCs) containing a large number of B cells.<sup>19</sup> The formation of these ectopic GCs may be triggered by a viral infection or other source of inflammation, but this has not been clearly demonstrated.<sup>19</sup>

Myasthenia gravis is the most common disorder of the neuromuscular junction, with an estimated prevalence of 14 to 20 per 100,000 people, approximately 36,000 to 60,000 cases in the United States.<sup>20</sup> Myasthenia gravis occurs at any age, but there tends to be a bimodal distribution to the age of onset, with an early peak in the second and third decades (female predominance) and a late peak in the sixth to eighth decade (male predominance).<sup>20</sup> It characteristically presents with fatigable weakness, often initially involving the ocular muscles and manifesting as intermittent ptosis and diplopia.<sup>21</sup> Ultimately, the disease generalizes throughout the body in two-thirds of patients, leading to weakness of bulbar, neck, limb, and respiratory muscles.<sup>21</sup>

The majority of patients with generalized MG, and roughly half of patients with purely ocular disease, harbor antibodies to skeletal muscle AChRs.<sup>21</sup> Patients with refractory generalized MG, representing approximately 10–15% of all patients with MG, do not respond to long-term treatment with corticosteroids or multiple immunosuppressant therapies (ISTs), or they have intolerable side-effects to these therapies or require ongoing treatment with either intravenous immunoglobulin or plasma exchange.<sup>4</sup> This heterogeneous patient population continues to have disease symptoms and persistent morbidities, despite substantial use of ISTs, including difficulties with speech, swallowing, and mobility, impairment of respiratory function, and extreme fatigue, with substantial

negative effects on activities of daily living and quality of life.<sup>4</sup> Patients with refractory generalized MG might also have frequent exacerbations, which can be life-threatening and require admission to hospital or intensive care, and cause episodes of respiratory failure that require mechanical ventilation.<sup>4</sup> The Myasthenia Gravis Foundation of America (MGFA) has developed a classification of MG depending on disease severity ranging from Class I (least severe) to Class V (most severe).<sup>22</sup> Class I disease is defined by the MGFA as any ocular weakness but no other symptoms.<sup>22</sup> Class V patients have worsening myasthenic weakness that requires intubation or noninvasive ventilation to avoid intubation.<sup>22</sup>

The myasthenia gravis activities of daily living (MG-ADL) is a patient-reported, physician administered scoring tool.<sup>23</sup> Eight domains (talking, chewing, swallowing, breathing, ability to brush teeth, ability to arise from chair, vision and eyelid droop) are scored on a scale of 0 (normal) to 3 (severe).<sup>23</sup> A total score of 24 is possible; higher scores indicate more disability.<sup>4</sup> A 2-point reduction in the MG-ADL is considered clinically meaningful improvement.<sup>23</sup> The Quantitative Myasthenia Gravis (QMG) score is a validated 13-item disease-severity physician-reported assessment tool.<sup>24</sup> This tool evaluates muscle strength based on quantitative testing of sentinel muscle groups: ocular (two items), facial (one item), bulbar (two items), gross motor (six items), axial (one item), and respiratory (one item).<sup>24</sup> The scores are not weighted, but each item is graded on a scale of 0 (no weakness) to 3 (severe weakness).<sup>24</sup> Total scores range from 0 to 39, higher scores represent greater disease burden.<sup>24</sup> A 3-point reduction in QMG total score considered a clinically meaningful improvement.<sup>25</sup>

As an immune-mediated disorder, MG can respond to several ISTs, such as corticosteroids, azathioprine, methotrexate, mycophenolate mofetil, tacrolimus and cyclosporine.<sup>22</sup> There is widespread variation in practice with respect to choice of IS agent since there is little literature comparing them.<sup>22</sup> Expert consensus from MGFA 2013 guidance support the use of azathioprine as a first-line immunosuppressive agent in MG based on sparse randomized clinical trial (RCT) evidence.<sup>22</sup> Evidence from RCTs supports the use of cyclosporine in MG, but potential serious adverse effects and drug interactions limit its use.<sup>22</sup> Although available RCT evidence does not support the use of mycophenolate and tacrolimus in MG, both are widely used, and one or both are recommended in several national MG treatment guidelines.<sup>22</sup>

In October 2019, the MGFA appointed a Task Force to update treatment guidance for MG, and a panel of 15 international experts was convened.<sup>26</sup> The previous recommendations for thymectomy were updated. Recommendations for the use of methotrexate, rituximab and eculizumab were re-evaluated based on available evidence.<sup>26</sup> Although robust evidence from RCTs is insufficient, oral methotrexate may be considered as a steroid-sparing agent in patients with generalized MG who have not tolerated or responded to steroid-sparing agents.<sup>26</sup> Rituximab should be considered as an early therapeutic option in patients with AchR antibody-positive generalized MG who have an unsatisfactory response to initial immunotherapy.<sup>26</sup> Eculizumab should be considered in the treatment of severe, refractory, AchR antibody-positive generalized MG.<sup>26</sup> The role of eculizumab in the treatment of MG is likely to evolve over time.<sup>26</sup> Until further data become available to allow comparisons of cost and efficacy with other treatments, eculizumab should be considered after trials of other immunotherapies have been unsuccessful in meeting treatment goals.<sup>26</sup>

## Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

### **NEW DRUG EVALUATION: Eculizumab**

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Eculizumab is a humanized monoclonal antibody that blocks terminal complement by binding to C5. Eculizumab prevents C5 conversion into C5a and C5b factors; thus, effectively inhibiting MAC formation and complement-mediated lysis.<sup>11</sup> FDA-approved indications for eculizumab include:

- Treatment of PNH to reduce hemolysis: approved March 2007
- Treatment of patients with aHUS to inhibit complement-mediated thrombotic microangiopathy: approved September 2011
- Treatment of MG in adult patients who are anti-acetylcholine receptor antibody positive: approved October 2017
- Treatment of NMOSD in adult patients who are anti-AQP4 antibody-positive: approved June 2019 (addressed in a separate class update presented to the P & T Committee, April 2021)

### **Clinical Efficacy:**

#### ***Paroxysmal Nocturnal Hemoglobinuria***

The efficacy and safety of eculizumab in adults with PNH was demonstrated in 2 multinational, phase 3 trials. In the double-blind TRIUMPH trial, patients with severe PNH disease were randomized to eculizumab or placebo and evaluated over 26 weeks (n=87).<sup>1</sup> The open-label, single-arm, 52 week SHEPHERD trial evaluated eculizumab in a broader PNH patient population (e.g., patients with thrombocytopenia and mild anemia; n=97).<sup>2</sup> The eculizumab intravenous regimen administered in both studies was an induction dosage of 600 mg every week for 4 weeks, then 900 mg at week 5 followed by a maintenance dosage of 900 mg every 2 weeks.<sup>1,2</sup>

The TRIUMPH study consisted of a 2-week screening period, an observation period of up to 3 months, and a 26-week treatment period.<sup>1</sup> Patients 18 years of age or older who had received at least four transfusions during the previous 12 months were eligible.<sup>1</sup> Patients who did not require a transfusion during the observation period were considered ineligible for study participation.<sup>1</sup> During the observation period a transfusion administered to a patient who had a hemoglobin level of 9 g per deciliter or less with symptoms or 7 g per deciliter or less with or without symptoms qualified the patient for the study and established the individual patient's hemoglobin set point. This set point would define each patient's hemoglobin stabilization and transfusion outcomes.<sup>1</sup> PNH type III erythrocyte proportion of 10% or more, platelet counts of at least 100,000/mm<sup>3</sup>, and lactate dehydrogenase (LDH) levels that were at least 1.5 times the upper limit of the normal range were also required.<sup>1</sup> Concomitant administration of erythropoietin, immunosuppressive drugs, corticosteroids, coumarins, low-molecular-weight heparins, iron supplements, and folic acid were permitted, provided that the doses were constant before and throughout the study.<sup>1</sup> Because persons who have a genetic deficiency of terminal complement proteins have an increased risk of meningococcal infections, all patients were vaccinated against *Neisseria meningitidis* with locally approved vaccines.<sup>1</sup>

The co-primary endpoints in the TRIUMPH trial were the stabilization of hemoglobin levels and the number of units of packed red cells transfused.<sup>1</sup> Patients received transfusions when they had symptoms resulting from anemia and their hemoglobin levels reached the individualized, predetermined set point.<sup>1</sup> Prespecified secondary end points included transfusion independence; hemolysis, as measured by the LDH value for the area under the curve from baseline to

26 weeks; and changes in the level of fatigue, as assessed from baseline to 26 weeks with the use of the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) instrument.<sup>1</sup> The FACIT-Fatigue scores can range from 0 to 52, with higher scores indicating improvement in fatigue.<sup>1</sup> The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) was used to assess quality of life. EORTC QLQ-C30 scores can range from 0 to 100, with higher scores on the global health status and functioning scales and lower scores on the symptom scales and single item measures indicating improvement.<sup>1</sup>

Stabilization of hemoglobin levels and the requirement for packed red cell transfusions were improved significantly more with eculizumab than with placebo after 26 weeks of treatment.<sup>1</sup> Forty-nine percent of all patients in the eculizumab group were transfusion independent compared with 0% of patients in the placebo group ( $p < 0.001$ ).<sup>1</sup> Hemolysis was also significantly reduced with eculizumab compared with placebo, as determined by lower mean levels of LDH in the eculizumab treatment group.<sup>1</sup> The median area under the concentration-time curve (AUC) for LDH was 86% lower with eculizumab than with placebo (58,587 vs. 411,822 U/L per day respectively;  $p < 0.001$ ).<sup>1</sup> Mean hemoglobin levels increased from 10.0 to 10.1 g/dL in the eculizumab group and decreased from 9.7 to 8.9 g/dL in the placebo group ( $p < 0.001$  eculizumab vs placebo).<sup>1</sup> Reticulocyte counts did not change significantly from baseline and remained elevated at week 26 in both groups.<sup>1</sup>

Consistent with improvements in other outcomes, by week 26, Health-Related Quality Of Life (HR-QOL) had improved significantly more in the eculizumab group than in the placebo group, as determined by the EORTC-QLQ-C30 and FACIT-Fatigue instruments ( $p < 0.001$  for both).<sup>1</sup> The EORTC-QLQ-C30 instrument demonstrated significant improvements in all five functioning scales and two of three symptom scales (fatigue [ $p < 0.001$ ], pain [ $p=0.002$ ] and nausea and vomiting [ $p=0.06$ ]).<sup>1</sup> Improvements in the single-item measures of dyspnea, loss of appetite and insomnia were also significantly ( $p < 0.01$ ) greater in the eculizumab group than in the placebo group, whereas changes in financial difficulties, constipation and diarrhea were not significant between groups.<sup>1</sup> Patients in the eculizumab group had a mean increase (improvement) in scores on the FACIT-Fatigue instrument of  $6.4 \pm 1.2$  points from baseline to week 26, whereas in the placebo group the mean score change of  $-4.0 \pm 1.7$  points during this period, for a total difference between the two groups of 10.4 points.<sup>1</sup>

In the open-label, single-arm SHEPHERD trial, the primary efficacy end point was hemolysis as assessed by LDH area under the curve (AUC).<sup>2</sup> All patients were vaccinated against *Neisseria meningitidis* at least 14 days prior to receiving the first dose of eculizumab.<sup>2</sup> Throughout the 52-week study, patients received transfusions with packed red blood cells if medically indicated.<sup>2</sup> The secondary efficacy end points included fatigue as measured by the FACIT-Fatigue instrument and LDH change from baseline.<sup>2</sup> The primary safety end points were adverse events, clinical laboratories, electrocardiogram (ECG) data, and vital signs.<sup>2</sup> The SHEPHERD study was designed to evaluate the safety and efficacy of eculizumab in PNH patients by relaxing the inclusion criteria of TRIUMPH study, to allow patients with minimal transfusion support and evidence of thrombocytopenia to participate.<sup>2</sup> PNH patients with at least one transfusion in the prior 24 months and at least 30,000 platelets/microliter were eligible for study enrollment.<sup>2</sup> Baseline transfusion requirements and platelet counts were statistically different between SHEPHERD and TRIUMPH ( $p < 0.001$  and  $p = 0.009$ , respectively).<sup>2</sup>

In the SHEPHERD trial, hemolysis was significantly improved from baseline with eculizumab treatment, as demonstrated by the reduction in LDH AUC (median change  $-632,264$  IU/L per day;  $p < 0.001$ ) after 52 weeks of treatment.<sup>2</sup> Mean LDH was significantly reduced by 87%, from 2201 IU/L at baseline to 297 IU/L (normal range is 80-225 U/L) at week 52 ( $p < 0.001$ ).<sup>2</sup> Eculizumab significantly reduced requirements for PRBC transfusions throughout the study.<sup>2</sup> During 52 weeks of eculizumab therapy, the median number of units transfused per patient was 0 compared with 8 units in the year prior to treatment ( $p < 0.001$ ).<sup>2</sup> The mean number of transfusions per patient was reduced from 12.3 to 5.9 units, a decrease of 52%.<sup>2</sup> Forty-nine (51%) patients were transfusion independent throughout 52 weeks of eculizumab therapy ( $p < 0.001$ ).<sup>2</sup> At week 52, the FACIT-Fatigue score had improved by 12.2 points ( $p < 0.001$ ) from baseline values.<sup>2</sup> Similarly, eculizumab significantly improved HR-QOL, as determined by the EORTC QLQ-C30 instrument, with global health status ( $p < 0.001$ ), all five scales for

functioning ( $p < 0.001$ ), all three symptom scales ( $p < 0.002$ ) and four of six single-item measures ( $p < 0.001$ ) compared with baseline.<sup>2</sup> More details for these trials are included in **Table 5**.

### **Trial Limitations**

The TRIUMPH trial was randomized, double-blinded and placebo-controlled in patients that had severe PNH. In contrast, the SHEPHERD trial was conducted in a broader range of PNH patients, but was single-armed, non-randomized, and open-label which introduced a higher risk of bias. Both trials were relatively short-term considering PNH is a chronic condition. Finally, both trials were designed, conducted and funded by the manufacturer.

### ***Myasthenia Gravis***

The randomized, placebo-controlled, double-blind, multicenter, phase 3 REGAIN study evaluated the safety and efficacy of eculizumab in 125 adults with IST refractory, AChR antibody-positive, generalized MG.<sup>4</sup> Eculizumab was administered in a dosing regimen evaluated in a phase 2 trial of MG patients: 900 mg every week for 4 weeks, 1200 mg at week, then 1200 mg every 2 weeks. The REGAIN study included patients aged  $\geq 18$  years with MG, a positive serological test for anti-AChR antibodies, impaired activities of daily living (i.e. MG-ADL score of 6 or greater) and MGFA class II–IV disease.<sup>4</sup> Patients were also required to have received 2 or more ISTs for 12 months without symptom control or 1 or more ISTs with chronic intravenous immunoglobulin or plasma exchange therapy (PLEX), without symptom control over 12 months.<sup>4</sup> Patients were randomized to eculizumab or placebo for 26 weeks.<sup>4</sup> Those receiving prior therapy with a cholinesterase inhibitor, oral corticosteroid or other ISTs were to continue treatment at the same dose and schedule throughout the study, unless an adjustment was needed due to a compelling medical reason.<sup>4</sup> Owing to the severity of disease, rescue medication (e.g. high-dose corticosteroids, intravenous immunoglobulin, plasma exchange therapy) was permitted at the physician's discretion.<sup>4</sup> All randomized patients were required to have been vaccinated against *Neisseria meningitides* with locally approved vaccines.<sup>4</sup>

The primary efficacy endpoint was the change from baseline to week 26 in MG-ADL total score.<sup>4</sup> Prespecified worst-rank ANCOVA of each patient was ranked from 1 (best) to 125 (worst), whereby the patient who had a myasthenia gravis crisis was ranked lowest and patients who received rescue therapy or dropped out of the study were ranked lowest according to time to event; all other patients were ranked higher according to change from baseline to week 26 or last observation carried forward (LOCF).<sup>4</sup> For the prespecified outcome change from baseline in worst-rank ANCOVA, 103 patients were ranked by the change from baseline (rank 1–103), 103 completed 26 weeks without rescue therapy, 22 were in the lowest-rank group, ranked by time to event (rank 104–125), one had a myasthenia gravis crisis and rescue therapy (rank 125), 17 other patients required rescue therapy by study end, and four discontinued for any reason.<sup>4</sup> The primary analysis showed no significant difference between eculizumab and placebo (least-squares mean rank 56.6 vs. 68.3; rank-based treatment difference -11.7; 95% CI -24.3 to 0.96;  $p = 0.0698$ ).<sup>4</sup>

A key secondary endpoint in REGAIN trial was the change from baseline in the QMG total score at Week 26. A statistically significant difference favoring eculizumab was observed in the mean change from baseline to Week 26 in QMG total scores (-4.6 points in the eculizumab-treated group compared with -1.6 points in the placebo-treated group;  $P = 0.001$ ).<sup>4</sup> In a sensitivity analyses, patients receiving eculizumab showed an initial improvement in MG-ADL total score by week 1, and QMG total score by week 2, with most of the treatment effect occurring by week 12 and sustained to week 26.<sup>4</sup> Change in MG-ADL (standard error of the mean) in eculizumab-treated patients was -4.2 compared with -2.3 in placebo-treated patients (Difference: -1.9; 95% CI -3.3 to -0.06;  $P = 0.006$ ).<sup>4</sup> The mean change from baseline at week 26 in MG-ADL and QMG score was greater with eculizumab than with placebo based on repeated-measures analyses with and without immunosuppressive therapies as a covariate.<sup>4</sup> The use of a worst-rank analytical approach proved to be an important limitation of this study since the secondary and sensitivity analyses results were inconsistent with the primary endpoint result; further research into the role of complement is needed.<sup>4</sup> More

details for this trial are included in **Table 5**. Based on the results of this trial, the MGFA recommends eculizumab should be considered in generalized MG patients with severe disease refractory to 2 or more ISTs or dependence on maintenance intravenous immunoglobulin or PLEX.<sup>26</sup>

### ***Atypical Hemolytic-Uremic Syndrome***

Eculizumab received FDA approval as an orphan drug via the FDA's accelerated approval pathway in 2011. The dosing regimen for eculizumab in aHUS consists of four, weekly 900 mg IV induction doses and then the patient is transitioned to maintenance dosing at 1200 mg IV every two weeks.<sup>6</sup> Two single-arm, multi-center, 26-week, phase 2 trials evaluated intravenous eculizumab inhibited complement-mediated thrombotic microangiopathy (TMA) in patients aged 12 years and older with aHUS.<sup>5</sup> Complete TMA response was defined as: hematologic normalization plus improvement in renal function (25% reduction from baseline in serum creatinine in two consecutive measurements for four or more weeks).<sup>5</sup> Trial C08-002 included patients with progressive TMA who were refractory to plasma exchange (n=17; 16 adults and 1 adolescent) while trial C08-003 included patients with chronic dependence on plasma exchange defined as no more than a 25% decrease in platelet counts during plasma exchange in the 8 weeks prior (n=20; 15 adults and 5 adolescents). At least 80% of patients achieved TMA-free status in both trials.<sup>5</sup> In addition, time-dependent improvements in renal function were observed.<sup>5</sup> At week 26, 65% and 25% of patients demonstrated complete TMA response in both trials.<sup>5</sup> At 26 weeks, the platelet count was significantly increased in patients with progressing thrombotic microangiopathy despite plasma exchange/infusion, and thrombotic microangiopathic event-free status was achieved in 80% of patients with a long disease duration and chronic kidney disease who received long-term plasma exchange.<sup>5</sup> Renal function also improved with eculizumab therapy in both studies.<sup>5</sup>

Due to the high risk of bias (single-arm, open label, non-randomized, small sample size) in both of these trials, they are not presented in **Table 5** (Comparative Evidence Table).

Limitation of Use: Soliris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).<sup>6</sup>

### **Clinical Safety:**

The most serious risk of terminal complement blockade is life-threatening meningococcal *infections* (roughly 0.5%/year or 5% after 10 years).<sup>3</sup> Thus, all patients treated with eculizumab should be vaccinated against *N. meningitidis* with the use of locally approved vaccines.<sup>3</sup> In severe PNH cases, especially those with concomitant thrombosis, administration of eculizumab and vaccination can be performed on the same day. In such cases, 2 weeks of prophylactic therapy with ciprofloxacin is recommended. In the United States eculizumab is available only through a restricted Risk Evaluation and Mitigation Strategy (REMS) program.<sup>6</sup>

The most common adverse events associated with eculizumab in the 26-week TRIUMPH<sup>1</sup> and 52-week SHEPHERD<sup>2</sup> studies in patients with PNH were headache (44%<sup>1</sup> and 53%<sup>2</sup>) and nasopharyngitis (23%<sup>1</sup> and 32%<sup>2</sup>). The majority of adverse events in both studies were mild to moderate in intensity.<sup>1</sup> More details about adverse events reported in the TRIUMPH trial compared to placebo are presented in **Table 1**.

In the REGAIN trial the most common adverse events in both groups were headache and upper respiratory tract infection (experienced by 10 patients [16%] for both events in the eculizumab group and 12 [19%] for both in the placebo group).<sup>4</sup> Myasthenia gravis exacerbations were reported by six (10%) patients in the eculizumab group and 15 (24%) in the placebo group.<sup>4</sup> Six (10%) patients in the eculizumab group and 12 (19%) in the placebo group required rescue therapy.<sup>4</sup> More details about adverse events reported in the REGAIN trial are presented in **Table 2**. Adverse effects reported in patients with aHUS are outlined in **Table 3**.

**Table 1. Adverse Reactions Reported in 10% or More of Eculizumab-Treated Patients with PNH and Greater than Placebo-Treated Patients<sup>6</sup>**

Reaction	Eculizumab (n=43)	Placebo (n=44)
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%)

**Table 2. Adverse Reactions Reported in 5% or More of Eculizumab-Treated Patients with MH and Greater than Placebo-Treated Patients<sup>6</sup>**

Reaction	Eculizumab (n=62)	Placebo (n=63)
Musculoskeletal Pain	9 (15%)	5 (8%)
Abdominal Pain	5 (8%)	3 (5%)
Peripheral Edema	5 (8%)	3 (5%)
Herpes Simplex Infections	5 (8%)	1 (2%)
Contusion	5 (8%)	2 (3%)
Pyrexia	4 (7%)	2 (3%)

**Table 3. Adverse Reactions Reported in 10% or More of Eculizumab-Treated Adults and Adolescents with aHUS<sup>6</sup>**

Reaction	Eculizumab (n=78)
Headache	32 (41%)
Hypertension	26 (33%)
Nasopharyngitis	21 (27%)
Nausea	18 (23%)
Cough	18 (23%)
Fatigue	10 (13%)
Back Pain	8 (10%)

Look-alike / Sound-alike Error Risk Potential: No medications identified

**Comparative Endpoints:**

Clinically Meaningful Endpoints:

- 1) Stabilize platelet count (aHUS)
- 2) Stabilize LDH count (aHUS)
- 3) Improve fatigue (PNH)
- 3) Improved functional status (PNH, aHUS, MG)
- 4) Serious adverse events
- 5) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) Reduced need for transfusions (PNH)
- 2) Stabilized hemoglobin level (PNH)
- 3) Improved MG-ADL score (MG)

**Table 4. Pharmacology and Pharmacokinetic Properties.<sup>6</sup>**

Parameter	
Mechanism of Action	Complement protein C5 inhibitor
Oral Bioavailability	N/A
Distribution and Protein Binding	Volume of Distribution: 5 L to 8 L; Protein Binding N/R
Elimination	aHUS: 14.6 mL/hour; PNH: 22 mL/hour
Half-Life	Ranges from 270 hours to 414 hours - aHUS: 291 hours; PNH: 272 hours
Metabolism	N/R

Abbreviations: aHUS = atypical hemolytic-uremic syndrome; kg = kilogram; mL = milliliters; L=liters; N/A=not applicable; N/R=not reported; PNH = paroxysmal nocturnal hemoglobinuria

**Table 5. Comparative Evidence Table.**

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Hillmen et al. <sup>1</sup>  TRIUMPH  DB, PC, MC, phase 3 RCT	1. Eculizumab 600 mg IV once a week x 4 weeks, followed by 900 mg 1 week later and then 900 mg every other week through week 26  2. Placebo	<u>Demographics:</u> 1. Male: 40% 2. Median age: 39 yo 3. Mean Hgb: 8 g/dL 4. Use of steroids: 34%  <u>Key Inclusion Criteria:</u> 1. Adults ≥18 yo who had received at least 4 transfusions in the previous 12 mos 2. PNH type 3 erythrocyte > 10% 3. Platelet count > 100,000/microliter 4. LDH > 1.5 ULN  <u>Key Exclusion Criteria:</u> 1. Receipt of transfusions during the 12 mos prior to study entry with a pre-transfusion mean hemoglobin > 10.5 g/dL 3. Complement deficiency 4. History of meningococcal disease 5. History of bone marrow transplant	<u>ITT:</u> 1. 43 2. 44  <u>PP:</u> 1. 41 2. 34  <u>Attrition:</u> 1. 2 (5%) 2. 10 (23%)	<u>Co-Primary Endpoints:</u> A. Number of patients with stabilization of hemoglobin levels in the absence of transfusions 1. 21 (49%) 2. 0 (0%) P<0.001  B. Median number of units of PRBC transfused per patient over 26 weeks 1. 0 units 2. 10 units P<0.001  <u>Secondary Endpoints:</u> A. Median LDL AUC level over 26 weeks 1. 58,587 U/L 2. 411,822 U/L Difference: 86% P<0.001  B. Change in FACIT-Fatigue score 1. +6.4 ± 1.2 points 2. - 4.0 ± 1.7 points Difference: +10.4 points P<0.001	49/2  NA  NA  NA	<u>Serious Adverse Effects</u> 1. 4 (9%) 2. 9 (21%)  <u>Headache</u> 1. 19 (44%) 2. 12 (27%)  <u>Nasopharyngitis</u> 1. 10 (23%) 2. 8 (18%)  <u>Upper Respiratory Tract Infection</u> 1. 6 (14%) 2. 10 (23%)  p-value and 95% CI NR for all		<b>Risk of Bias (low/high/unclear):</b> <u>Selection Bias:</u> Low. Randomized 1:1 via central IVRS. Stratified according to number of units of PRBC transfused in the previous 12 mos. Baseline characteristics were balanced between groups. <u>Performance Bias:</u> Low. Double-blind study design: participants and investigators were masked to treatment assignment. Protocol does not describe if eculizumab and placebo were similar in appearance. <u>Detection Bias:</u> Unclear. Protocol does not describe if eculizumab and placebo were similar in appearance. <u>Attrition Bias:</u> High. More patients in the placebo arm withdrew due to perceived lack of efficacy. <u>Reporting Bias:</u> Unclear. Protocol unavailable online. <u>Other Bias:</u> Unclear. Funded by Alexion Pharmaceuticals. The authors and the sponsor were jointly responsible for the trial design and the development of the protocol.  <b>Applicability:</b> <u>Patient:</u> Strict inclusion criteria limited enrollment to patients with severe PNH. <u>Intervention:</u> Dosing evaluated in phase 2 open label trial. <u>Comparator:</u> No other approved treatments available; placebo comparator is appropriate. <u>Outcomes:</u> Reduction in transfusion frequency is appropriate endpoint for PNH. <u>Setting:</u> 34 sites in the United States, Canada, Europe, and Australia

<p>2.Brodsky, et al.<sup>2</sup></p> <p>SHEPHERD</p> <p>OL, phase 3 study</p>	<p>1. Eculizumab 600 mg IV once a week x 4 weeks, followed by 900 mg 1 week later and then 900 mg every other week through week 52</p>	<p><u>Demographics:</u></p> <ol style="list-style-type: none"> <li>1. Male: 50%</li> <li>2. Median age: 41 yo</li> <li>3. Race-White: 91%</li> <li>4. Median PNH duration: 4.9 yrs</li> <li>5. Baseline platelet count range: 23-355/microliter</li> <li>6. Baseline LDH range: 537-5245 U/L</li> </ol> <p><u>Key Inclusion Criteria:</u></p> <ol style="list-style-type: none"> <li>1. Adults &gt; 18 yo who had received at least 1 transfusion in the previous 24 mos</li> <li>2. PNH type 3 erythrocyte &gt; 10%</li> <li>3. Platelet count &gt; 30,000/microliter</li> <li>4. LDH &gt; 1.5 ULN</li> </ol> <p><u>Key Exclusion Criteria:</u></p> <ol style="list-style-type: none"> <li>1. Complement deficiency</li> <li>2. History of meningococcal disease</li> <li>3. History of bone marrow transplant</li> </ol>	<p><u>ITT:</u></p> <p>1. 97</p> <p><u>PP:</u></p> <p>1. 96</p> <p><u>Attrition:</u></p> <p>1. 1 (1%)</p>	<p><u>Primary Endpoint:</u> Median reduction in LDH AUC over 52 weeks compared to baseline</p> <ol style="list-style-type: none"> <li>1. -632,264 U/L/day P&lt;0.001</li> </ol> <p><u>Secondary Endpoints:</u></p> <p>A. Mean LDH level (normal range: 103 to 223 U/L)</p> <ol style="list-style-type: none"> <li>1. Baseline: 2,201 ± 105 U/L</li> <li>2. 52 weeks: 297 ± 21 U/L P&lt;0.001</li> </ol> <p>B. Mean Change in FACIT-Fatigue score from baseline to 52 weeks</p> <ol style="list-style-type: none"> <li>1. +12.2 ± 1.1 P&lt;0.001</li> </ol>	<p>NA</p> <p>NA</p> <p>NA</p>	<p><u>Headache</u></p> <ol style="list-style-type: none"> <li>1. 51 (53%)</li> </ol> <p><u>Nasopharyngitis</u></p> <ol style="list-style-type: none"> <li>1. 31 (32%)</li> </ol> <p><u>Upper Respiratory Tract Infection</u></p> <ol style="list-style-type: none"> <li>1. 29 (30%)</li> </ol>		<p><b>Risk of Bias (low/high/unclear):</b></p> <p><u>Selection Bias:</u> High. Open-label, single armed study.</p> <p><u>Performance Bias:</u> High. Open-label design.</p> <p><u>Detection Bias:</u> High. Single-arm study.</p> <p><u>Attrition Bias:</u> Low. 1 patient withdrew due to adverse effect unrelated to study drug.</p> <p><u>Reporting Bias:</u> Low. Protocol available at clinicaltrials.gov</p> <p><u>Other Bias:</u> High. Trial funded by Alexion Pharmaceuticals. The authors and the sponsor were jointly responsible for the trial design and the development of the protocol.</p> <p><b>Applicability:</b></p> <p><u>Patient:</u> Inclusion criteria allowed minimal transfusion requirements or evidence of thrombocytopenia, allowing for broader enrollment of adults with PNH.</p> <p><u>Intervention:</u> Dosing evaluated in phase 2 open label trial.</p> <p><u>Comparator:</u> Single arm trial: no comparator evaluated.</p> <p><u>Outcomes:</u> Safety over 52 week and efficacy as assessed by change in LDH.</p> <p><u>Setting:</u> Several centers in the U.S.</p>
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<p>3. Howard, JF et al.<sup>4</sup></p> <p>REGAIN</p> <p>DB, PG, PC, MC phase 3 RCT over 26 weeks</p>	<p>1. Eculizumab 900 mg IV once a week x 4 weeks, followed by 1200 mg 1 week later and then 1200 mg every other week through week 26</p> <p>2. Matched placebo</p>	<p><u>Demographics:</u></p> <p>1. Female Gender: 66%</p> <p>2. Race: White: 76% Asian: 15%</p> <p>2. Duration of MG: 8.2 years</p> <p>3. Age: 47 yo</p> <p>4. MG-ADL score: 10.2</p> <p>5. MGFA disease classification IIa or IIIa: 50% IIb or IIIb: 41%</p> <p><u>Key Inclusion Criteria:</u></p> <p>1. Adults aged 18 yo and older with MG and positive anti-AchR antibodies</p> <p>2. MG Clinical Classification: II-IV</p> <p>3. MG-ADL score <math>\geq</math> 6</p> <p>4. Failed IST treatment</p> <p><u>Key Exclusion Criteria:</u></p> <p>1. History of thymoma or other neoplasm of the thymus</p> <p>2. Thyectomy less than 12 mos prior to study</p> <p>3. Use of IVIG or plasma exchange less than 4 weeks prior to study</p> <p>4. Use of rituximab less than 6 mos prior to screening</p>	<p><u>ITT:</u></p> <p>1. 62</p> <p>2. 63</p> <p><u>PP:</u></p> <p>1. 57</p> <p>2. 61</p> <p><u>Attrition:</u></p> <p>1. 5 (8%)</p> <p>2. 3 (5%)</p>	<p><u>Primary Endpoint:</u></p> <p>Mean-ranked change in MG-ADL score from baseline to week 26 (least-squares mean rank)</p> <p>1. 56.6</p> <p>2. 68.3</p> <p>Difference: -11.7</p> <p>95% CI -24.3 to 0.96</p> <p>P=0.0698</p> <p><u>Secondary Endpoints</u></p> <p>A. Change in MG-ADL (standard error of the mean)</p> <p>1. -4.2</p> <p>2. -2.3</p> <p>Difference: -1.9</p> <p>95% CI -3.3 to -0.06</p> <p>P=0.006</p> <p>B. Change from baseline in the QMG total score at Week 26 (least-squares mean)</p> <p>1. -4.6</p> <p>2. -1.6</p> <p>Difference -3.0</p> <p>95% CI -4.6 to -1.3</p> <p>P=0.001</p>	<p>NS</p> <p>NA</p> <p>NA</p>	<p><u>Serious Adverse Events</u></p> <p>1. 9 (15%)</p> <p>2. 18 (29%)</p> <p><u>Headache</u></p> <p>1. 10 (16%)</p> <p>2. 12 (19%)</p> <p><u>Upper Respiratory Infection:</u></p> <p>1. 10(16%)</p> <p>2. 12 (19%)</p> <p>95% CI and p-value NR for all</p>	<p><b>Risk of Bias (low/high/unclear):</b></p> <p><u>Selection Bias:</u> Low. Patients randomized 1:1 to eculizumab or placebo via IVRS system. Patients stratified according to disease severity. Treatment groups were generally well matched regarding demographic characteristics, disease status, and medical history.</p> <p><u>Performance Bias:</u> Low. Patients, investigators, staff, and outcome assessors were masked to treatment assignment.</p> <p><u>Detection Bias:</u> Low. Placebo was matched to eculizumab.</p> <p><u>Attrition Bias:</u> Low. Attrition rates were low in both arms.</p> <p><u>Reporting Bias:</u> Low. Protocol available on-line. Outcomes reported as pre-specified.</p> <p><u>Other Bias:</u> High. Trial funded by Alexion Pharmaceuticals. The funder of the study had a role in study design, study conduct, and data collection. The funding source was responsible for the statistical analysis plan and protocol as well as the final clinical study report. In addition, the medical writer was an employee of the funding source and additional employees provided a review of the manuscript.</p> <p><b>Applicability:</b></p> <p><u>Patient:</u> Representative of MG population who had failed prior IST.</p> <p><u>Intervention:</u> Dosing evaluated in phase 2 trial.</p> <p><u>Comparator:</u> Placebo is an appropriate comparator.</p> <p><u>Outcomes:</u> Quality of life is a reasonable outcome to evaluate therapy using the validated MG-ADL. Secondary outcomes were focused on safety endpoints.</p> <p><u>Setting:</u> 76 hospitals and specialized clinics in 17 countries across North America, Latin America, Europe, and Asia</p>
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**Abbreviations** [alphabetical order]: AchR = Acetylcholine Receptor; ARR = absolute risk reduction; AUC = Area Under the Curve; CI = confidence interval; DB = double blind; dL = deciliter; FACIT-F Score = Functional Assessment of Chronic Illness Therapy-Fatigue; IST = Immunosuppressive Therapy; ITT = intention to treat; IVIg = Intravenous Immunoglobulin; IVRS = interactive voice-response system; LDH = lactate dehydrogenase; MC = Multi-Center; MG-ADL = Myasthenia Gravis Activities of Daily Living; MG = Myasthenia Gravis; MGFA = Myasthenia Gravis Foundation of America; mITT = modified intention to treat; mos = months; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OL = open-label; PG = Parallel Group; PC = Placebo-Controlled; PNH = Paroxysmal Nocturnal Hemoglobinuria; PP = per protocol; PRBC = packed red blood cells; QMG = Quantitative Myasthenia Gravis; RCT= Randomized Controlled Trial; ULN = upper limit normal; U = unit; yo = years old

## **NEW DRUG EVALUATION: Ravulizumab**

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

### **Clinical Efficacy:**

Ravulizumab (Ultomiris™), a humanized monoclonal antibody, is a complement C5 inhibitor FDA-approved for the treatment of PNH and aHUS. In December 2018, the US Food and Drug administration approved ravulizumab for the treatment of PNH. Efficacy data for the use of ravulizumab in adults with PNH are described and evaluated below in **Table 9**. Treatment of adults and pediatric patients one month of age and older with aHUS to inhibit complement-mediated thrombotic microangiopathy (TMA) received FDA approval October 2020.<sup>10</sup>

Like eculizumab, the first-generation C5 inhibitor, ravulizumab binds specifically and with high affinity to the complement protein C5, thereby preventing formation of the terminal complement complex C5b-9, which mediates cell lysis.<sup>27</sup> The drug was developed by re-engineering eculizumab to create a novel longer-acting antibody, requiring less frequent infusions than eculizumab.<sup>27</sup> Ravulizumab has a 3 to 4 times longer half-life compared to eculizumab and requires dosing every eight weeks.<sup>27</sup> In adults with PNH and aHUS, ravulizumab is administered via intravenous infusion according to weight, commencing with a loading dose and followed 2 weeks later with a maintenance dose, which is continued once every 8 weeks.<sup>10</sup> For patients switching from eculizumab to ravulizumab, a loading dose should be administered 2 weeks after the last eculizumab infusion, followed by a maintenance dose 2 weeks later, then once every 8 weeks.<sup>10</sup>

### **Paroxysmal Nocturnal Hemoglobinuria**

FDA approval for the use of ravulizumab in the treatment of PNH was based on the results of two phase 3 clinical trials. In the first trial, ALXN1210-PNH-301, ravulizumab was administered to C5 inhibitor-naïve PNH patients,<sup>7</sup> and in the second trial, ALXN1210-PNH-302,<sup>8</sup> stable PNH patients previously treated with eculizumab were enrolled in the study. Patients in both studies had been vaccinated against meningococcal infections at least 3 years prior to treatment. In both multi-center, randomized, open-label, phase 3 noninferiority trials, ravulizumab treatment was initiated with a loading dose on day 1, followed by maintenance doses on day 15 and every 8 weeks thereafter; all doses were based on weight.<sup>7</sup> The intravenous ravulizumab group received a loading dose (2400 mg for patients weighing  $\geq 40$  to  $< 60$  kg, 2700 mg for patients  $\geq 60$  kg to  $< 100$  kg, and 3000 mg for patients  $\geq 100$  kg) on day 1, followed by maintenance doses of ravulizumab (3000 mg for patients  $\geq 40$  to  $< 60$  kg, 3300 mg for patients  $\geq 60$  to  $< 100$  kg, and 3600 mg for patients  $\geq 100$  kg) on day 15 and every 8 weeks thereafter.<sup>7</sup> Patients assigned to eculizumab received induction doses of 600 mg on days 1, 8, 15, and 22 only in the 301 trial, followed by maintenance dosing of 900 mg on day 29 and every 2 weeks thereafter per the approved PNH dosing regimen.<sup>7</sup>

In the trial in C5 inhibitor-naïve patients, those with LDH levels  $\geq 1.5$  times the upper limit of normal (ULN) and at least one PNH symptom were eligible for inclusion. Co-primary efficacy end points were proportion of patients remaining transfusion-free and LDH normalization.<sup>7</sup> Secondary end points were percent

change from baseline in LDH, change from baseline in FACIT–Fatigue score, proportion of patients with breakthrough hemolysis, and stabilized hemoglobin levels.<sup>7</sup> The study consisted of a 4-week screening period and a 26-week randomized treatment period to evaluate the efficacy and safety of ravulizumab versus eculizumab, followed by an extension period of up to 2 years, during which all patients receive ravulizumab.<sup>7</sup> Patients were stratified into 6 groups based on transfusion history (0, 1–14, or >14 units of packed red blood cells in the 1 year before the first dose of study drug) and LDH screening level (1.5 to <3 times the ULN or  $\geq 3 \times$  ULN).<sup>7</sup> Enrollment of patients without a history of transfusion in the past year was capped at 20%. Hemoglobin levels were evaluated before randomization and within 5 days before study drug initiation; patients were transfused, if necessary, to reach the protocol-specified hemoglobin level.<sup>7</sup>

In C5 inhibitor–naïve patients, transfusion avoidance in ravulizumab (n = 125) and eculizumab (n = 121) treatment arms was achieved in 73.6% versus 66.1% of patients, respectively, with a between-group difference of 6.8% (95% CI – 4.66 to +18.14;  $p < 0.0001$  for noninferiority).<sup>7</sup> The lower bound of the 95% CI was greater than the protocol-specified noninferiority margin of –20%.<sup>7</sup> The noninferiority margin for the coprimary endpoint of LDH normalization was based on a previous randomized, placebo-controlled study of eculizumab<sup>1</sup> and adjusted to the observed baseline LDH normalization of recent phase 1b and 2 studies, calculated with a weighted average of the proportions of LDH normalization from day 29 to day 183.<sup>7</sup> LDH normalization was achieved in 53.6% versus 49.4% of patients (adjusted odds ratio 1.19; 95% CI 0.80–1.77;  $p < 0.0001$  for noninferiority).<sup>7</sup> The lower bound of the 95% CI was greater than the protocol-specified noninferiority margin of 0.39.<sup>7</sup> Ravulizumab was also noninferior to eculizumab in all key secondary endpoints: percent reduction in LDH (–76.8% vs. –76.0%; difference –0.83%; 95% CI, –5.21 to 3.56), change in FACIT–Fatigue score (7.07 vs. 6.40; difference 0.67; 95% CI, –1.21 to 2.55), breakthrough hemolysis (4.0% vs. 10.7%; difference –6.7%; 95% CI –14.21 to 0.18), and stabilized hemoglobin (68.0% vs. 64.5%; difference 2.9%; 95% CI –8.80 to 14.64).<sup>7</sup>

The eculizumab pretreatment trial recruited stable patients who had received eculizumab for 6 months or more before study entry, with LDH levels of  $\leq 1.5 \times$  ULN at screening.<sup>8</sup> In this phase 3, open-label, noninferiority, multicenter study, 195 PNH patients on labeled-dose (900 mg every 2 weeks) eculizumab for greater than 6 months were randomly assigned 1:1 to switch to ravulizumab (n = 97) or continue eculizumab (n = 98).<sup>8</sup> The study consisted of a 4-week screening period followed by a 26-week randomized treatment period and an extension period during which all patients received ravulizumab for up to 2 years.<sup>8</sup> Patients were stratified according to transfusion history.<sup>8</sup> Patients assigned to the ravulizumab treatment group received weight-based dosing: a loading dose on day 1 followed by maintenance doses of ravulizumab on day 15 and every 8 weeks thereafter.<sup>8</sup> Patients assigned to eculizumab received a maintenance dosage of 900 mg every 2 weeks.<sup>8</sup> At the end of the 26-week treatment period, ravulizumab-treated patients continued weight-based maintenance dosing of ravulizumab, whereas eculizumab-treated patients were switched to open-label ravulizumab for the extension period.<sup>8</sup>

The primary efficacy end point was hemolysis, as measured by percentage change in LDH from baseline to day 183.<sup>8</sup> Key secondary end points included proportion of patients with breakthrough hemolysis, change in FACIT–Fatigue score, transfusion avoidance, and stabilized hemoglobin.<sup>8</sup> In stable patients previously treated with eculizumab, the mean percentage change in LDH in ravulizumab and eculizumab treatment arms was – 0.82% versus + 8.39% [treatment difference of 9.21% (95% CI – 0.42 to 18.84);  $p < 0.0006$  for noninferiority].<sup>8</sup> The lower bound of the 95% CI for the difference was –0.42%, which did not exceed the protocol-specified noninferiority margin of –15%, indicating that ravulizumab is noninferior to eculizumab.<sup>8</sup> In 191 patients completing 183 days of treatment, ravulizumab was noninferior to eculizumab for outcomes of breakthrough hemolysis (difference, 5.1 [95% CI, –8.89 to 18.99]), change in FACIT–Fatigue score (difference, 1.47 [95% CI, –0.21 to 3.15]), transfusion avoidance (difference, 5.5% [95% CI, –4.27 to 15.68]), and stabilized hemoglobin (difference, 1.4% [95% CI, –10.41 to 13.31];  $p < 0.0006$  for noninferiority for all end points).<sup>8</sup>

Transfusion avoidance in ravulizumab and eculizumab treatment arms in the trial in patients previously treated with eculizumab was achieved in 87.6% of patients receiving ravulizumab and 82.7% receiving eculizumab [treatment difference 5.5% (95% CI – 4.27 to 15.68)].<sup>8</sup> Results of this trial also demonstrated that patients with PNH can be effectively and safely switched from eculizumab every 2 weeks to ravulizumab every 8 weeks.<sup>8</sup> Compared to eculizumab, ravulizumab

was noninferior for achieving transfusion independence, LDH normalization, the proportion of patients with breakthrough hemolysis, change in serum free C5, and fatigue score.<sup>7</sup> Safety and tolerability of were similar, and no meningococcal infections occurred with either therapy.

### Trial Limitations

Both of the phase 3 trials that evaluated the efficacy of ravulizumab were noninferiority trials, which are not designed to show superiority of one drug over another. In both trials ravulizumab provided similar efficacy as eculizumab in treating PNH in patients that were C5 naïve or who had previous exposure to C5 treatment. Both trials were relatively short-term considering PNH is a chronic condition. Finally, both trials were designed, conducted and funded by the manufacturer.

### Atypical Hemolytic Uremic Syndrome

A prospective, open-label, phase 3 trial evaluated the efficacy and safety of ravulizumab in adults with aHUS.<sup>9</sup> In this global, multicenter, single arm study, patients received intravenous ravulizumab as a weight-based loading dose on day 1, followed by weight-based maintenance doses on day 15 and every 8 weeks thereafter.<sup>9</sup> After 26 weeks of treatment with ravulizumab, complete thrombotic microangiopathy response (TMA; primary efficacy endpoint) was seen in 53.6% of complement-inhibitor naïve adult patients with aHUS (n =56).<sup>9</sup> A complete TMA response encompasses hematological normalization [reduced thrombocytopenia (evidenced by normalization of platelet count) and hemolysis (normalization of LDH levels)] and improved renal function (≥ 25% improvement in serum creatinine level from baseline).<sup>9</sup> Thrombocytopenia was reduced in 83.9% (95% CI 73.4–94.4%) of patients, LDH levels were normalized in 76.8% (95% CI 64.8–88.7%) and improved renal function was seen in 58.9% (95% CI 45.2–72.7%).<sup>9</sup> Due to the high risk of bias (single-arm, open label, non-randomized, small sample size) in this trial, it is not presented in **Table 9** (Comparative Evidence Table).

### Clinical Safety:

In the United States, ravulizumab is available only through a restricted Risk Evaluation and Mitigation Strategy (REMS) program.<sup>10</sup> Ravulizumab prescribing information contains a black box warning due to an increased risk of life-threatening and fatal meningococcal infections.<sup>10</sup> Common adverse effects associated with ravulizumab administration may include upper respiratory tract infection and headache.<sup>10</sup> Serious adverse reactions were reported in 15 (6.8%) patients with PNH receiving ravulizumab.<sup>10</sup> The serious adverse reactions in patients treated with ravulizumab included hyperthermia and pyrexia.<sup>10</sup> No serious adverse reaction was reported in more than 1 patient treated with ravulizumab.<sup>10</sup> Adverse reactions reported in clinical trials in patients with PNH and aHUS are presented in **Tables 6 and 7**.

**Table 6. Adverse Reactions Reported in 5% or More of Ravulizumab-Treated Patients with PNH Compared with Eculizumab<sup>10</sup>**

Adverse Reaction	Ravulizumab (n=222)	Eculizumab (n=219)
Upper Respiratory Tract Infection	86 (39%)	86 (39%)
Headache	71 (32%)	57 (26%)
Diarrhea	19 (9%)	12 (5%)
Nausea	19 (9%)	19 (9%)
Pyrexia	15 (7%)	18 (8%)
Abdominal Pain	13(6%)	16 (7%)

**Table 7. Adverse Reactions Reported in 10% or More of Ravulizumab-Treated Patients with aHUS<sup>10</sup>**

Adverse Reaction	Ravulizumab (n=16)
Pyrexia	8 (50%)
Upper Respiratory Tract Infection	7 (44%)
Diarrhea	6 (38%)
Headache	5 (31%)
Abdominal Pain	3(19%)
Nausea	2 (13%)

Look-alike / Sound-alike Error Risk Potential: No medications identified

**Comparative Endpoints:**

Clinically Meaningful Endpoints:

- 1) Hemolysis
- 2) Percentage of patients with breakthrough hemolysis
- 3) Anemia
- 4) Quality of life
- 4) Serious adverse events
- 5) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) Proportion of patients that were transfusion free (PNH)
- 2) Percentage change in LDH levels from baseline (PNH)
- 3) Complete thrombotic microangiopathy response (aHUS)

**Table 8. Pharmacology and Pharmacokinetic Properties<sup>10</sup>**

Parameter	
Mechanism of Action	Complement C5 Inhibitor
Oral Bioavailability	N/A
Distribution and Protein Binding	Volume of Distribution = 5.34 L (PNH) and 5.22 L (aHUS)
Elimination	29.5 L/day (PNH) and 53.3 L/day (aHUS)
Half-Life	49.7 days (PNH) and 51.8 days (aHUS)
Metabolism	N/R

Abbreviations: aHUS = atypical Hemolytic Uremic Syndrome; L=Liters; N/A = Not Applicable; N/R = Not Reported; PNH=Paroxysmal Nocturnal Hemoglobinuria

**Table 9. Comparative Evidence Table**

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Lee JW, et al. <sup>7</sup>  OL, MC, phase 3 NI study over 183 days	1. Weight based ravulizumab induction followed by maintenance dose administered IV every 8 weeks  2. Eculizumab 900 mg IV administered every 2 weeks	<u>Demographics:</u> 1. Male: 55% 2. Age: 46 yo 3. Race: White: 38% Asian: 52% Japanese: 14% Black: 2% 4. Percent of patients with transfusions received 1 year prior to first study dose: 13%  <u>Key Inclusion Criteria:</u> 1. Adults ≥ 18 yo with PNH, naive to C5 treatment 2. LDH ≥ 1.5 ULN  <u>Key Exclusion Criteria:</u> 1. Previous C5 exposure 2. Weight < 40 kg 3. History bone marrow transplantation 4. Platelet count < 30,000/ $\mu$ L	<u>ITT:</u> 1. 125 2. 121  <u>PP:</u> 1. 125 2. 119  <u>Attrition:</u> 1. 0 (0%) 2. 3 (2%)	<u>Co-Primary Endpoint:</u> a. Proportion of patients that were transfusion-free at 26 weeks 1. 92 (73.6%) 2. 80 (66.1%) Difference: 6.8% (95% CI, -4.66 to +18.14) P<0.0001 for NI  b. LDH normalization from days 29 through 183 1. 67 (53.6%) 2. 60 (49.4%) OR: 1.19 95% CI 0.80 to 1.77 P<0.0001 for NI  <u>Secondary Endpoints:</u> a. LSM change in LDH 1. -76.84 2. -76.02 Mean Difference: -0.83% 95% CI -5.21 to 3.56 P<0.0001 for NI  b. LSM change in FACIT-Fatigue score from baseline 1. 7.70 2. 6.40 Difference: 0.67 95% CI -1.21 to 2.55 P<0.0001 for NI	N/A for all due to NI study design	<u>Serious Adverse Effects</u> 1. 4 (3%) 2. 8(7%)  <u>Adverse Effects:</u> 1. 110 (88%) 2. 105 (87%)  <u>Headache:</u> 1. 45 (36%) 2. 40 (33%)  <u>Nasopharyngitis</u> 1. 11 (8.8%) 2. 18 (14.9%)  <u>Upper Respiratory Infection</u> 1. 13 (10%) 2. 7 (6%)  95% CI and p-value NR for all	N/A	<b>Risk of Bias (low/high/unclear):</b> <u>Selection Bias:</u> Unclear. Randomized 1:1 to receive ravulizumab or eculizumab. Method of randomization not described. Baseline characteristics balanced between groups. <u>Performance Bias:</u> High. Study was not blinded. <u>Detection Bias:</u> High. Open label study design <u>Attrition Bias:</u> Low. Attrition rates were low in both arms. <u>Reporting Bias:</u> Low. Protocol available online at clinicaltrials.gov. Outcomes reported as prespecified. <u>Other Bias:</u> Unclear. Funded by Alexion Pharmaceuticals, Inc. The authors and the sponsor were jointly responsible for the trial design and the development of the protocol  <b>Applicability:</b> <u>Patient:</u> Patients naive to C5 therapy <u>Intervention:</u> Dosing evaluated in phase 2 trial <u>Comparator:</u> Noninferiority comparison with eculizumab. <u>Outcomes:</u> Transfusion requirements and elevated hemolysis (LDH≥1.5 x ULN) are significant measures of PNH disease severity. <u>Setting:</u> 123 centers in 25 countries

<p>2. Kulaesekaraj AG, et al.<sup>8</sup></p> <p>OL, MC, phase 3 NI study over 183 days</p>	<p>1. Weight based ravulizumab induction followed by maintenance dose administered IV every 8 weeks</p> <p>2. Eculizumab 900 mg IV administered every 2 weeks</p>	<p><b>Demographics:</b></p> <p>1. Male: 50%</p> <p>2. Age: 48 yo</p> <p>3. Race:</p> <p>White: 57%</p> <p>Asian: 22%</p> <p>Japanese: 6%</p> <p>Black: 4%</p> <p><b>Key Inclusion Criteria:</b></p> <p>1. Adults ≥ 18 yo with PNH, previously treated with eculizumab</p> <p>2. LDH level ≤1.5 x the ULN (ULN: 246 U/L)</p> <p><b>Key Exclusion Criteria:</b></p> <p>1. LDH &gt;2 x ULN</p> <p>2. Platelet count &lt; 30,000/μL</p> <p>3. Weight &lt; 40 kg</p> <p>4. History bone marrow transplantation</p>	<p><b>ITT:</b></p> <p>1. 97</p> <p>2. 98</p> <p><b>PP:</b></p> <p>1. 96</p> <p>2. 95</p> <p><b>Attrition:</b></p> <p>1. 1 (1%)</p> <p>2. 3 (3%)</p>	<p><b>Primary Endpoint:</b></p> <p>LSM percentage change in LDH from baseline through day 183</p> <p>1. -0.82%</p> <p>2. +8.4%</p> <p>Difference: 9.2%</p> <p>95% CI: -0.42% to +18.8%</p> <p>p&lt;0.0006 for NI</p> <p><b>Secondary Endpoints:</b></p> <p>a. Proportion of patients that were transfusion-free</p> <p>1. 85 (87.6%)</p> <p>2. 74 (75.2%)</p> <p>Difference: 5.5%</p> <p>(95% CI, -4.3 to +15.7)</p> <p>P&lt;0.0006 for NI</p> <p>b. LSM change in FACIT-Fatigue score from baseline</p> <p>1. 2.0</p> <p>2. 0.54</p> <p>Difference: 1.5</p> <p>95% CI -0.2 to 3.2</p> <p>P&lt;0.0006 for NI</p>	<p>N/A for all due to NI study design</p>	<p><b>Adverse Effects:</b></p> <p>1. 85 (87.6%)</p> <p>2. 86 (87.8%)</p> <p><b>Headache:</b></p> <p>1. 26 (26.8%)</p> <p>2. 17 (17.3%)</p> <p><b>Nasopharyngitis</b></p> <p>1. 21 (21.6%)</p> <p>2. 20 (20.4%)</p> <p><b>Upper Respiratory Infection</b></p> <p>1. 18 (18.6%)</p> <p>2. 10 (10.2%)</p> <p>95% CI and p-value for all</p>		<p><b>Risk of Bias (low/high/unclear):</b></p> <p><b>Selection Bias:</b> Unclear. Assigned 1:1 to ravulizumab or eculizumab. Method of randomization not described. Baseline demographics balanced between groups</p> <p><b>Performance Bias:</b> High. Study was not blinded.</p> <p><b>Detection Bias:</b> High. Open label study design.</p> <p><b>Attrition Bias:</b> Low. Attrition rates were low in both arms.</p> <p><b>Reporting Bias:</b> Low. Protocol available online at clinicaltrials.gov. Outcomes reported as prespecified.</p> <p><b>Other Bias:</b> Unclear. Funded by Alexion Pharmaceuticals, Inc. The authors and the sponsor were jointly responsible for the trial design and the development of the protocol.</p> <p><b>Applicability:</b></p> <p><b>Patient:</b> Patients previously exposed to C5 therapy</p> <p><b>Intervention:</b> Dosing evaluated in phase 2 trial</p> <p><b>Comparator:</b> Noninferiority comparison with eculizumab.</p> <p><b>Outcomes:</b> Hemolysis (as assessed by LDH levels) is a significant measure of PNH disease severity</p> <p><b>Setting:</b> 49 centers in 11 countries</p>
<p><b>Abbreviations:</b> ARR = absolute risk reduction; C5 = complement 5; CI = confidence interval; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; ITT = intention to treat; IV = intravenous; LDH = lactate dehydrogenase; LSM = least squares mean; MC = multi-center; N = number of subjects; NA = not applicable; NI = Non-Inferiority; NNH = number needed to harm; NNT = number needed to treat; OL = open-label; PP = per protocol; ULN = upper limit of normal</p>								

## References:

1. Hillmen P, Young NS, Schubert J, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 2006;355(12):1233-1243.
2. 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;111(4):1840-1847.
3. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. *Blood*. 2014;124(18):2804-2811.
4. Howard JF, Utsugisawa K, Benatar M, et al. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. *The Lancet Neurology*. 2017;16(12):976-986.
5. Legendre CM, Licht C, Muus P, et al. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. *N Engl J Med*. 2013;368(23):2169-2181.
6. Soliris (eculizumab) Solution for Intravenous Infusion Prescribing Information. Boston, MA; Alexion Pharmaceuticals, Inc. 11/2020.
7. Lee JW, Sicre de Fontbrune F, Wong Lee Lee L, et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. *Blood*. 2019;133(6):530-539.
8. Kulasekararaj AG, Hill A, Rottinghaus ST, et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. *Blood*. 2019;133(6):540-549.
9. Rondeau E, Scully M, Ariceta G, et al. The long-acting C5 inhibitor, Ravulizumab, is effective and safe in adult patients with atypical hemolytic uremic syndrome naïve to complement inhibitor treatment. *Kidney Int*. 2020;97(6):1287-1296.
10. Ultomiris™ (Ravulizumab-cwvz): US Prescribing Information. Boston, MA; Alexion Pharmaceuticals Inc. 10/2020.
11. Shah N, Bhatt H. Paroxysmal Nocturnal Hemoglobinuria. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2020.
12. Parker C, Omine M, Richards S, et al. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. *Blood*. 2005;106(12):3699-3709.
13. Röth A, Maciejewski J, Nishimura JI, Jain D, Weitz JI. Screening and diagnostic clinical algorithm for paroxysmal nocturnal hemoglobinuria: Expert consensus. *Eur J Haematol*. 2018;101(1):3-11.
14. Gulbis B, Eleftheriou A, Angastiniotis M, et al. Epidemiology of rare anaemias in Europe. *Adv Exp Med Biol*. 2010;686:375-396.
15. Schrezenmeier H, Muus P, Socié G, et al. Baseline characteristics and disease burden in patients in the International Paroxysmal Nocturnal Hemoglobinuria Registry. *Haematologica*. 2014;99(5):922-929.
16. Nishimura JI, Kanakura Y, Ware RE, et al. Clinical course and flow cytometric analysis of paroxysmal nocturnal hemoglobinuria in the United States and Japan. *Medicine (Baltimore)*. 2004;83(3):193-207.
17. Raina R, Krishnappa V, Blaha T, et al. Atypical Hemolytic-Uremic Syndrome: An Update on Pathophysiology, Diagnosis, and Treatment. *Ther Apher Dial*. 2019;23(1):4-21.
18. Gilhus NE. Myasthenia Gravis. *N Engl J Med*. 2016;375(26):2570-2581.
19. Guptill JT, Soni M, Meriggioli MN. Current Treatment, Emerging Translational Therapies, and New Therapeutic Targets for Autoimmune Myasthenia Gravis. *Neurotherapeutics*. 2016;13(1):118-131.
20. Myasthenia Gravis Foundation of America Classification of Myasthenia Gravis <https://myasthenia.org/Professionals/Clinical-Overview-of-MG> Accessed February 22, 2021.
21. Silvestri NJ, Wolfe GI. Myasthenia gravis. *Semin Neurol*. 2012;32(3):215-226.

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22. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis. *Executive summary*. 2016;87(4):419-425.
  23. Wolfe GI, Herbelin L, Nations SP, Foster B, Bryan WW, Barohn RJ. Myasthenia gravis activities of daily living profile. *Neurology*. 1999;52(7):1487-1489.
  24. Jaretzki A, 3rd, Barohn RJ, Ernstoff RM, et al. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. *Neurology*. 2000;55(1):16-23.
  25. Katzberg HD, Barnett C, Merkies IS, Bril V. Minimal clinically important difference in myasthenia gravis: outcomes from a randomized trial. *Muscle & nerve*. 2014;49(5):661-665.
  26. Narayanaswami P, Sanders DB, Wolfe G, et al. International Consensus Guidance for Management of Myasthenia Gravis: 2020 Update. *Neurology*. 2021;96(3):114-122.
  27. McKeage K. Ravulizumab: First Global Approval. *Drugs*. 2019;79(3):347-352.

## Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
eculizumab	SOLIRIS	INTRAVEN	VIAL	
ravulizumab-cwvz	ULTOMIRIS	INTRAVEN	VIAL	

## Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to January Week 2 2021, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 15, 2021.

1. *exp Hemoglobinuria, Paroxysmal/* 1691
2. *exp Atypical Hemolytic Uremic Syndrome/* 687
3. *exp Myasthenia Gravis/* 7030
4. *eculizumab.mp.* 1792
5. *ravulizumab.mp.* 39
6. *1 or 2 or 3* 9374
7. *4 or 5* 1799
8. *6 and 7* 713
9. *limit 8 to (english language and humans)* 632
10. *limit 9 to (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial protocol or clinical trial or controlled clinical trial or guideline or meta-analysis or randomized controlled trial or "systematic review")* 38

## Appendix 3: Prescribing Information Highlights

### 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) injection, for intravenous use  
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 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).

#### RECENT MAJOR CHANGES

Indications and Usage (1.4)	06/2019
Dosage and Administration (2.4, 2.5)	06/2019
Dosage and Administration (2.5, 2.6, 2.7)	07/2018
Warnings and Precautions (5.1, 5.2)	07/2018

#### 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).

#### DOSAGE AND ADMINISTRATION

For intravenous infusion only

PNH Dosage Regimen: (2.2)

aHUS Dosage Regimen: (2.3)

gMG and NMOSD Dosage Regimen: (2.4)

#### DOSAGE 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).

#### 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 ( $\geq 20\%$ ) are: headache, diarrhea, 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 ( $\geq 10\%$ ) is: musculoskeletal pain (6.1).

The most frequently reported adverse reactions in the NMOSD placebo-controlled trial ( $\geq 10\%$ ) 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](http://www.fda.gov/medwatch).

See 17 PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 06/2019

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ULTOMIRIS<sup>2</sup> (ravulizumab-cwvz) injection, for intravenous use  
Initial U.S. Approval: 2018

### WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

See full prescribing information for complete boxed warning

Life-threatening meningococcal infections/sepsis have occurred in patients treated with ULTOMIRIS 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 ULTOMIRIS, unless the risks of delaying ULTOMIRIS 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 infection. Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.

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

### RECENT MAJOR CHANGES

Dosing and Administration (2.5)

10/2020

### INDICATIONS AND USAGE

ULTOMIRIS is a complement inhibitor indicated for:

- the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) (1).
- the treatment of adults and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA) (1).

### Limitations of Use:

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

### DOSAGE AND ADMINISTRATION

See Full Prescribing Information for instructions on dosage, preparation, and administration (2.1, 2.2, 2.3, 2.4, 2.5).

### DOSAGE FORMS AND STRENGTHS

Injection:

- 300 mg/30 mL (10 mg/mL) in a single-dose vial (3).
- 300 mg/3 mL (100 mg/mL) in a single-dose vial (3).
- 1,100 mg/11 mL (100 mg/mL) in a single-dose vial (3).

### CONTRAINDICATIONS

ULTOMIRIS is contraindicated in:

- Patients with unresolved *Neisseria Meningitidis* infection (4).
- Patients who are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying ULTOMIRIS treatment outweigh the risks of developing a meningococcal infection (4, 5.1).

### WARNINGS AND PRECAUTIONS

- Other Infections: Use caution when administering ULTOMIRIS to patients with any other systemic infection (5.2).
- Infusion-Related Reactions: Monitor patients during infusion, interrupt for reactions, and institute appropriate supportive measures (5.5).

### ADVERSE REACTIONS

Most common adverse reactions in patients with PNH (incidence  $\geq 10\%$ ) were upper respiratory tract infection and headache (6.1).

Most common adverse reactions in patients with aHUS (incidence  $\geq 20\%$ ) were upper respiratory tract infection, diarrhea, nausea, vomiting, headache, hypertension and pyrexia (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](http://www.fda.gov/medwatch).

See 17 PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2020

Appendix 4: Prior Authorization Criteria

**Eculizumab (Soliris®)**

**Goal(s):**

- Restrict use to OHP funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Eculizumab is FDA-approved for:
  - Neuromyelitis Optica Spectrum Disorder (NMOSD) in adult patients who are anti-AQP4-IgG-antibody positive
  - Reducing hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH)
  - Inhibiting complement-mediated thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome (aHUS)
  - Treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor (AChR) antibody positive

**Length of Authorization:**

Up to 12 months

**Requires PA:**

- Soliris® (eculizumab) physician administered claims

**Covered Alternatives:**

- Current PMPDP preferred drug list per OAR 410-121-0030 at [www.orpdl.org](http://www.orpdl.org)
- Searchable site for Oregon FFS Drug Class listed at [www.orpdl.org/drugs/](http://www.orpdl.org/drugs/)

<b>Approval Criteria</b>		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	<b>Yes:</b> Go to #3	<b>No:</b> Pass to RPh. Deny; not funded by the OHP.
3. Is this request for continuation of therapy?	<b>Yes:</b> Go to <b>Renewal Criteria</b>	<b>No:</b> Go to #4

<b>Approval Criteria</b>		
4. Has the patient been vaccinated against <i>Neisseria meningitides</i> according to current Advisory Committee on Immunization Practice (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies?	<b>Yes:</b> Go to #5	<b>No:</b> Pass to RPh. Deny; medical appropriateness
5. Is the diagnosis one of the following: <ul style="list-style-type: none"> <li>• Neuromyelitis Optica Spectrum Disorder (NMOSD) in an adult who is anti-aquaporin-4 (AQP4) antibody positive,</li> <li>• Paroxysmal Nocturnal Hemoglobinuria (PNH),</li> </ul> <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> <li>• atypical Hemolytic Uremic Syndrome (aHUS)? (Note: Eculizumab is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).</li> </ul>	<b>Yes:</b> Go to #6	<b>No:</b> Go to #7
6. Does the requested dosing align with the FDA- approved dosing ( <b>Table 1</b> )?	<b>Yes:</b> Approve for 12 months	<b>No:</b> Pass to RPh. Deny; medical appropriateness
7. Is the request for a diagnosis of myasthenia gravis ACh Receptor (AChR) antibody-positive?	<b>Yes:</b> Go to # 8	<b>No:</b> Pass to RPh. Deny; medical appropriateness

Approval Criteria		
8. Has the patient tried: <ul style="list-style-type: none"> <li>at least 2 or more immunosuppressant therapies (e.g., glucocorticoids in combination with azathioprine or mycophenolate mofetil or cyclosporine or tacrolimus or methotrexate or rituximab) for 12 months without symptom control OR</li> <li>at least 1 or more nonsteroidal immunosuppressant with maintenance intravenous immunoglobulin once monthly or plasma exchange therapy (PLEX) over 12 months without symptom control?</li> </ul>	<b>Yes:</b> Go to #9	<b>No:</b> Pass to RPh. Deny; medical appropriateness
9. Is the Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score $\geq 6$ ?	<b>Yes:</b> Approve for 12 months	<b>No:</b> Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there objective documentation of treatment benefit from baseline? Appropriate measures will vary by indication (e.g., hemoglobin stabilization, decreased transfusions, symptom control or improvement, functional improvement, etc.).	<b>Yes:</b> Approve for 12 months  Document baseline assessment and physician attestation received.	<b>No:</b> Pass to RPh. Deny; medical appropriateness

**Table 1. FDA-Approved Indications and Dosing for Eculizumab<sup>1</sup>**

	Eculizumab (Soliris <sup>®</sup> )
<b>FDA-approved Indications</b>	<ul style="list-style-type: none"> <li>Neuromyelitis Optica Spectrum Disorder (NMOSD) in adult patients who are anti-AQP4-IgG-antibody</li> <li>Reducing hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH)</li> <li>Inhibiting complement-mediated thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome (aHUS)</li> <li>Treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor antibody positive</li> </ul>

<b>Recommended NMOSD dose in patients 18 yo and older</b>	900 mg IV every week x 4 weeks, followed by 1200 mg IV for the fifth dose 1 week later, then 1200 mg IV every 2 weeks thereafter		
<b>Recommended PNH dose in patients 18 yo and older</b>	600 mg IV every week x 4 weeks, followed by 900 mg IV for the fifth dose 1 week later, then 900 mg IV every 2 weeks thereafter		
<b>Recommended aHUS dose in patients less than 18 yo</b>	<b>Body Weight</b> 5 kg to 9 kg 10 kg to 19 kg 20 kg to 29 kg 30 kg to 39 kg ≥ 40 kg	<b>Induction Dose</b> 300 mg weekly x 1 dose 600 mg weekly x 1 dose 600 mg weekly x 2 doses 600 mg weekly x 2 doses 900 mg weekly x 4 doses	<b>Maintenance Dose</b> 300 mg at week 2; then 300mg every 3 weeks 300 mg at week 2; then 300mg every 2 weeks 600 mg at week 3; then 600mg every 2 weeks 900 mg at week 3; then 900 mg every 2 weeks 1200 mg at week 5; then 1200 mg every 2 weeks
<b>Recommended aHUS dose in patients 18 yo and older</b>	900 mg IV every week x 4 weeks, followed by 1200 mg IV for the fifth dose 1 week later, then 1200 mg IV every 2 weeks thereafter		
<b>Recommended generalized MG dose</b>	900 mg IV every week x 4 weeks, followed by 1200 mg IV for the fifth dose 1 week later, then 1200 mg IV every 2 weeks thereafter		
<b>Dose Adjustment in Case of Plasmapheresis, Plasma Exchange, or Fresh Frozen Plasma Infusion</b>	Dependent on most recent eculizumab dose: refer to prescribing information for appropriate dosing (300 mg to 600 mg)		

1. Soliris (eculizumab) Solution for Injection Prescribing Information. Boston, MA: Alexion Pharmaceuticals, Inc. 11/2020.

*P&T/DUR Review: 4/21 (DM)  
Implementation: 5/1/21*

## Ravulizumab (Ultomiris®)

### Goal(s):

- Restrict use to OHP funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Ravulizumab is FDA-approved for:
  - Reducing hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH)
  - Inhibiting complement-mediated thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome (aHUS)

### Length of Authorization:

Up to 12 months

### Requires PA:

- Ultomiris® (Ravulizumab) physician administered claims

### Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at [www.orpdl.org](http://www.orpdl.org)
- Searchable site for Oregon FFS Drug Class listed at [www.orpdl.org/drugs/](http://www.orpdl.org/drugs/)

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	<b>Yes:</b> Go to #3	<b>No:</b> Pass to RPh. Deny; medical appropriateness
3. Is this request for continuation of therapy?	<b>Yes:</b> Go to <b>Renewal Criteria</b>	<b>No:</b> Go to # 4
4. Has the patient been vaccinated against <i>Neisseria meningitides</i> according to current Advisory Committee on Immunization Practice (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies?	<b>Yes:</b> Go to #5	<b>No:</b> Pass to RPh. Deny; medical appropriateness

Approval Criteria		
5. Is the diagnosis for a patient with Paroxysmal Nocturnal Hemoglobinuria (PNH) or for a patient at least 1 month of age or older with atypical Hemolytic Uremic Syndrome (aHUS)? (Note: Ravulizumab is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).	<b>Yes:</b> Go to #6	<b>No:</b> Pass to RPh. Deny; medical appropriateness
6. Does the requested dosing align with the FDA-approved dosing ( <b>Table 1</b> )?	<b>Yes:</b> Approve for 12 months	<b>No:</b> Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there objective documentation of treatment benefit from baseline? Appropriate measures will vary by indication (e.g., hemoglobin stabilization, decreased transfusions, symptom improvement, functional improvement, etc.).	<b>Yes:</b> Approve for 12 months  Document baseline assessment and physician attestation received.	<b>No:</b> Pass to RPh. Deny; medical appropriateness

**Table 1. FDA-Approved Indications and Dosing for Ravulizumab<sup>1</sup>**

	Ravulizumab		
<b>FDA-approved Indications</b>	<ul style="list-style-type: none"> <li>Reducing hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH)</li> <li>Inhibiting complement-mediated thrombotic microangiopathy in patients aged 1 month and older with atypical hemolytic uremic syndrome (aHUS)</li> </ul>		
<b>Recommended aHUS dose in patients less than 18 yo</b>	<b>Body Weight</b>	<b>Loading Dose</b>	<b>Maintenance Dose</b>
	5 to 9 kg	600 mg	300 mg every 4 weeks
	10 to 19 kg	600 mg	600 mg every 4 weeks
	20 to 29 kg	900 mg	2100 mg every 8 weeks
<b>Recommended aHUS dose in patients 18 yo and older</b>	<b>Body Weight</b>	<b>Loading Dose</b>	<b>Maintenance Dose</b>
	40 to 59 kg	2,400 mg	3,000 mg every 8 weeks
	60 to 99 kg	2,700 mg	3,300 mg every 8 weeks
	≥ 100 kg	3,000 mg	3,600 mg every 8 weeks

<b>Recommended PNH dose in patients 18 yo and older</b>	<b>Body Weight</b>	<b>Loading Dose</b>	<b>Maintenance Dose</b>
	40-59 kg	2,400 mg	3,000 mg every 8 weeks
	60-99 kg	2,700 mg	3,300 mg every 8 weeks
	≥ 100 kg	3,000 mg	3,600 mg every 8 weeks

1. Ultomiris™ (Ravulizumab-cwvz) Solution for Intravenous Infusion Prescribing Information. Boston, MA: Alexion Pharmaceuticals Inc. 10/2020.

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*P&T/DUR Review: 4/2021 (dm)*  
*Implementation: 5/1/21*