RXADVANCE
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Clinical Policy Title:	eculizumab
Policy Number:	RxA.491
Drug(s) Applied:	Soliris®
Original Policy Date:	03/06/2020
Last Review Date:	12/07/2020
Line of Business Policy Applies to:	All lines of business

Background

Eculizumab (Soliris®) is a complement inhibitor. It is indicated for the treatment of:

- Patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis.
- Patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy.
- Adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AchR) antibody positive.
- Adult patients with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody positive.

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

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
eculizumab (Soliris®)	PNH	IV infusion: 600 mg weekly for the first 4 weeks, followed by 900 mg for the fifth dose 1 week later, then 900 mg every 2 weeks thereafter	900 mg/dose
	aHUS	IV infusion: 900 mg weekly for the first 4 weeks, followed by 1,200 mg for the fifth dose 1 week later, then 1,200 mg every 2 weeks thereafter	1,200 mg/dose
	gMG, NMOSD	IV infusion: 900 mg every 7 days for the first 4 weeks, followed by a single dose of 1,200 mg 7 days after the fourth dose, and then 1,200 mg every 2 weeks thereafter	1,200 mg/dose

Dosage Forms

- Single-dose vials: 300 mg/30 mL

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

I. Initial Approval Criteria

A. Paroxysmal Nocturnal Hemoglobinuria (must meet all)**:**

1. Diagnosis of PNH;
2. Prescribed by or in consultation with a hematologist;
3. Age 18 years of age or older;
4. Flow cytometry demonstrates one of the following (a or b):
   a. At least 10% PNH type III red cells;
   b. Greater than 50% of glycosylphosphatidylinositol-anchored proteins (GPI-AP)-deficient polymorphonuclear cells
5. Member meets one of the following (a or b):
   a. History of one (1) or more red blood cell transfusions in the past 24 months and (i or ii):
      i. Documentation of hemoglobin less than 7 g/dL in members without anemia symptoms;
      ii. Documentation of hemoglobin less than 9 g/dL in members with anemia symptoms;
   b. Occurrence of a thromboembolic event;
6. Dose does not exceed 600 mg per week for the first 4 weeks, followed by 900 mg for the fifth dose 1 week later, then 900 mg every 2 weeks thereafter.

Approval duration
Commercial: 6 months
Medicaid: 6 months

B. Atypical Hemolytic Uremic Syndrome (must meet all)**:**

1. Diagnosis of aHUS (i.e., complement-mediated HUS);
2. Prescribed by or in consultation with a hematologist or nephrologist;
3. Age 2 months of age or older;
4. Member has signs of TMA as evidenced by all of the following (a, b, and c):
   a. Platelet count of 150 x 10^9 /L or less;
   b. Hemolysis such as an elevation in serum lactate dehydrogenase (LDH);
   c. Serum creatinine above the upper limits of normal or member requires dialysis;
5. Absence of Shiga toxin-producing E. coli infection;
6. Dose does not exceed 900 mg per week for the first 4 weeks, followed by 1,200 mg for the fifth dose 1 week later, then 1,200 mg every 2 weeks thereafter.

Approval duration
Commercial: 6 months
Medicaid: 6 months

C. Generalized Myasthenia Gravis (must meet all)**:**

1. Diagnosis of gMG;
2. Prescribed by or in in consultation with a neurologist;
3. Age 18 years of age or older;
4. Myasthenia Gravis-Activities of Daily Living (MG-ADL) score 6 or higher at baseline;
5. Myasthenia Gravis Foundation of America Clinical Classification (MGFA) Class II to IV;
6. Member has positive serologic test for anti-AChR antibodies;
7. Failure of a corticosteroid (see Appendix B) unless contraindicated or clinically significant adverse effects

are experienced;
8. Failure of a cholinesterase inhibitor (*see Appendix B*) unless contraindicated or clinically significant adverse effects are experienced;
9. Failure of two immunosuppressive therapies (see Appendix B) unless contraindicated or clinically significant adverse effects are experienced;
10. Dose does not exceed 900 mg per week for the first 4 weeks, followed by 1,200 mg for the fifth dose 1 week later, then 1,200 mg every 2 weeks thereafter.

Approval duration
Commercial: 6 months
Medicaid: 6 months

D. Neuromyelitis Optica Spectrum Disorder (must meet all)**:**
1. Member has a clinically confirmed diagnosis of neuromyelitis optica spectrum disorder and is anti-aquaporin-4 antibody positive;
2. Member has clinical evidence of at least one (1) documented relapse in the past 12 months;
3. Prescribed by or in in consultation with a neurologist;
4. Age 18 years of age or older;
5. Failure of rituximab at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
6. Member is treated with eculizumab as monotherapy or in combination with or in combination with immunosuppressive therapy (i.e. azathioprine, mycophenolate or oral corticosteroids);
7. Member is not being treated with eculizumab for acute treatment of NMOSD relapse; and
8. Does not exceed 900 mg per week for the first 4 weeks, followed by 1,200 mg for the fifth dose 1 week later, then 1,200 mg every 2 weeks thereafter.

Approval duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy

A. Paroxysmal Nocturnal Hemoglobinuria (must meet all):
1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member is responding positively to therapy as evidenced by, including but not limited to, improvement in any of the following parameters:
   a. Improved measures of intravascular hemolysis (e.g., normalization of lactate dehydrogenase [LDH]);
   b. Reduced need for red blood cell transfusions;
   c. Increased or stabilization of hemoglobin levels;
   d. Less fatigue;
   e. Improved health-related quality of life;
   f. Fewer thrombotic events;
3. If request is for a dose increase, new dose does not exceed 900 mg every 2 weeks.

Approval duration
Commercial: 6 months
Medicaid: 6 months

B. Atypical Hemolytic Uremic Syndrome (must meet all):
1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;

2. Member is responding positively to therapy as evidenced by, including but not limited to, improvement in any of the following parameters:
   a. Improved measures of intravascular hemolysis (e.g., normalization of LDH);
   b. Increased or stabilized platelet counts;
   c. Improved or stabilized serum creatinine or estimated glomerular filtration rate (eGFR);
   d. Reduced need for dialysis;
3. If request is for a dose increase, new dose does not exceed 1,200 mg every 2 weeks.

Approval duration
Commercial: 6 months
Medicaid: 6 months

C. Generalized Myasthenia Gravis (must meet all)**:**
1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member is responding positively to therapy as evidenced by a 2-point reduction in MG-ADL total score;
3. If request is for a dose increase, new dose does not exceed 1,200 mg every 2 weeks.

Approval duration
Commercial: 6 months
Medicaid: 6 months

D. Neuromyelitis Optica Spectrum Disorder (must meet all)**:**
1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member is responding positively to therapy (i.e. increase in time to relapse of NMOSD is indicative of efficacy); and
3. If request is for a dose increase, new dose does not exceed 1,200 mg every 2 weeks.

Approval duration
Commercial: 6 months
Medicaid: 6 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
AchR: Acetylcholine Receptor
aHUS: Atypical Hemolytic Uremic Syndrome
AQP-4: Aquaporin-4
EDSS: Expanded Disability Status Scale
FDA: Food and Drug Administration
gMG: Generalized myasthenia gravis
LDH: Lactate dehydrogenase
MG-ADL: Myasthenia Gravis-Activities of Daily Living
MGFA: Myasthenia Gravis Foundation of America Clinical Classification
PNH: Paroxysmal nocturnal hemoglobinuria
PO: By Mouth
STEC-HUS: Shiga toxin E. coli Related Hemolytic Uremic Syndrome
TID: Three Times Daily
TMA: Thrombotic Microangiopathy
NMOSD: Neuromyelitis Optica Spectrum Disorder

APPENDIX B: Therapeutic Alternatives

Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Corticosteroids		
betamethasone	Oral: 0.6 to 7.2 mg PO per day	7.2 mg/day
dexamethasone	Oral: 0.75 to 9 mg/day PO per day	9 mg/day
methylprednisolone	Oral: 12 to 20 mg PO per day; increase as needed by 4 mg every 2-3 days until there is marked clinical improvement or to a maximum of 40 mg/day	40 mg/day
prednisone	Oral: 15 mg/day to 20 mg/day; increase by 5 mg every 2-3 days as needed.	60 mg/day
Cholinesterase Inhibitors		
pyridostigmine (Mestinon®, Regonol®)	Oral immediate release: 600 mg daily in divided doses (range, 60-1,500 mg daily in divided doses) Oral sustained release: 180-540 mg once daily or BID IV or IM: 2 mg every 2-3 hours	See regimen
neostigmine (Bloxiverz®)	Oral: 15 mg PO TID. The daily dosage should be gradually increased at intervals of 1 or more days. The usual maintenance dosage is 15-375 mg/day (average 150 mg) IM or SC: 0.5 mg based on response to therapy	See regimen
Immunosuppressants		
azathioprine (Imuran®)	Oral: 50 mg once daily for 1 week, then increase gradually to 2 to 3 mg/kg/day	3 mg/kg/day
mycophenolate mofetil (Cellcept®)*	Oral: Dosage not established. 1 gram BID has been used with adjunctive corticosteroids or other non-steroidal immunosuppressive medications	2 g/day
cyclosporine (Sandimmune®)*	Oral: initial dose of cyclosporine (Non- modified), 5 mg/kg/day in 2 divided doses	5 mg/kg/day
Rituxan® (rituximab), Ruxience™ (rituximab-pvvr), Truxima® (rituximab-abbs)*†	IV: 375 mg/m^2 once a week for 4 weeks; an additional 375 mg/m^2 dose may be given every 1 to 3 months afterwards **NMOSD** IV: 375 mg/m^2 per week for 4 weeks as induction, followed by 375 mg/m^2 biweekly every 6 to 12 months	See regimen

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

*Off-label

†*Prior authorization may be required for rituximab*

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - unresolved serious Neisseria meningitidis infection,
  - patients who are not currently vaccinated against Neisseria meningitidis, unless the risks of delaying eculizumab treatment outweigh the risks of developing a meningococcal infection.

- Boxed Warning(s):
  - serious meningococcal infections.

APPENDIX D: General Information

- Eculizumab is only available through a REMS (Risk Evaluation and Mitigation Strategy) program due to the risk of life-threatening and fatal meningococcal infection. Patients should be vaccinated with a meningococcal vaccine at least 2 weeks prior to receiving the first dose of eculizumab and revaccinated according to current medical guidelines for vaccine use. Patients should be monitored for early signs of meningococcal infections, evaluated immediately if infection is suspected, and treated with antibiotics if necessary.
- The Advisory Committee on Immunization Practices (ACIP)'s recommendations regarding the meningococcal vaccine are found here: http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mening.html.
- Examples of positive response to therapy include:
  - PNH: improved measures of intravascular hemolysis (e.g., normalization of lactate dehydrogenase [LDH]), reduced need for red blood cell transfusions, less fatigue, improved health-related quality of life, fewer thrombotic events;
  - aHUS: decreased need for plasma therapy (plasma exchange or plasma infusion), decreased need for dialysis, increased glomerular filtration rate, normalization of platelet counts and/or LDH levels;
  - gMG: A 2-point reduction in MG-ADL total score is considered a clinically meaningful improvement. The scale can be accessed here: http://www.myasthenia.org/HealthProfessionals/EducationalMaterials.aspx
- The MGFA classification has some subjectivity in it when it comes to distinguishing mild (Class II) from moderate (Class III) and moderate (Class III) from severe (Class IV). Furthermore, it is insensitive to change from one visit to the next.
- Aquaporin-4 (AQP-4): AQP-4-IgG-seroposotive status is confirmed with the use of commercially available cell-binding kit assay.

References

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10. Lebreton C, Bacchetta J, Dijoud F, et al. C3 glomerulopathy and eculizumab: A report on four paediatric cases. Pediatr Nephrol. 2017;32(6):1023-1028. Accessed September 28, 2020.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/01/2020	03/06/2020
Policy was reviewed: 1. Formatting updated. 2. Clinical policy title was updated. 3. Initial approval criteria for approval updated. 4. Continued criteria for approval updated. 5. References were reviewed and updated.	09/28/2020	12/07/2020