

Clinical Policy: Eculizumab (Soliris)

Reference Number: ERX.SPA.201

Effective Date: 01.11.17

Last Review Date: 02.22

Line of Business: Commercial, Medicaid

[Revision Log](#)

See **Important Reminder** at the end of this policy for important regulatory and legal information.

Description

Eculizumab (Soliris[®]) is a complement inhibitor.

FDA Approved Indication(s)

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

Policy/Criteria

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

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions[™] that Soliris is **medically necessary** when the following criteria are met:

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 \geq 18 years;
4. Flow cytometry shows detectable glycosylphosphatidylinositol (GPI)-deficient hematopoietic clones or \geq 10% PNH cells;
5. Member meets one of the following (a or b):
 - a. History of \geq 1 red blood cell transfusion in the past 24 months and (i or ii):
 - i. Documentation of hemoglobin $<$ 7 g/dL in members without anemia symptoms;
 - ii. Documentation of hemoglobin $<$ 9 g/dL in members with anemia symptoms;
 - b. History of thrombosis;
6. Soliris is not prescribed concurrently with Empaveli[™] or Ultomiris[®], unless the member is in a 4-week period of cross-titration between Soliris and Empaveli;
**Provider must submit attestation of the presence or absence of concomitant Empaveli therapy*
7. 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: 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 \geq 2 months;
4. Member has signs of TMA as evidenced by all of the following (a, b, and c):
 - a. Platelet count \leq $150 \times 10^9/L$;
 - 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. Documentation that member does not have either of the following:
 - a. A disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13 (ADAMTS13) deficiency;
 - b. STEC-HUS;
6. Soliris is not prescribed concurrently with Ultomiris;
7. 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: 6 months

C. Generalized Myasthenia Gravis (must meet all):

1. Diagnosis of gMG;
2. Prescribed by or in consultation with a neurologist;
3. Age \geq 18 years;
4. Myasthenia Gravis-Activities of Daily Living (MG-ADL) score \geq 6 at baseline;
5. Myasthenia Gravis Foundation of America (MGFA) clinical classification of 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 clinically significant adverse effects are experienced or all are contraindicated;
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: 6 months

D. Neuromyelitis Optica Spectrum Disorder (must meet all):

1. Diagnosis of NMOSD;
2. Prescribed by or in consultation with a neurologist;
3. Age \geq 18 years;
4. Member has positive serologic test for anti-AQP4 antibodies;
5. Member has experienced at least one relapse within the previous 12 months;
6. Member meets one of the following (a or b):
 - a. History of at least two relapses during the previous 12 months;
 - b. History of three relapses during the previous 24 months
7. Baseline expanded disability status scale (EDSS) score of \leq 7;
8. Failure of rituximab (*Ruxience™ is preferred*) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
**Prior authorization may be required for rituximab*
9. Soliris is not prescribed concurrently with rituximab, Enspryng™, or Uplizna®;
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: 6 months

E. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Paroxysmal Nocturnal Hemoglobinuria and Atypical Hemolytic Uremic Syndrome (must meet all):

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy as evidenced by, including but not limited to, improvement in any of the following parameters:
 - a. PNH:
 - i. Improved measures of intravascular hemolysis (e.g., normalization of LDH);
 - ii. Reduced need for red blood cell transfusions;
 - iii. Increased or stabilization of hemoglobin levels;
 - iv. Less fatigue;
 - v. Improved health-related quality of life;
 - vi. Fewer thrombotic events;
 - b. aHUS:
 - i. Improved measures of intravascular hemolysis (e.g., normalization of LDH);
 - ii. Increased or stabilized platelet counts;
 - iii. Improved or stabilized serum creatinine or estimated glomerular filtration rate (eGFR);
 - iv. Reduced need for dialysis;
3. Soliris is not prescribed concurrently with (a or b):
 - a. PNH: Empaveli or Ultomiris;
 - b. aHUS: Ultomiris;
4. If request is for a dose increase, new dose does not exceed (a or b):
 - a. For PNH: 900 mg every 2 weeks;
 - b. For aHUS: 1,200 mg every 2 weeks.

Approval duration: 6 months

B. Generalized Myasthenia Gravis (must meet all):

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
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: 6 months

C. Neuromyelitis Optica Spectrum Disorder (must meet all):

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy – including but not limited to improvement or stabilization in any of the following parameters:
 - a. Frequency of relapse rate;
 - b. EDSS;
 - c. Visual acuity;
3. Soliris is not prescribed concurrently with rituximab, Enspryng, or Uplizna;
4. If request is for a dose increase, new dose does not exceed 1,200 mg every 2 weeks.

Approval duration: 6 months

D. Other diagnoses/indications (must meet 1 or 2):

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

- A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents;
- B. STEC-HUS;
- C. Antiphospholipid syndrome (D68.61);
- D. Unspecified nephritic syndrome with other morphologic changes (N05.8).

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AchR: anti-acetylcholine receptor	NMOSD: neuromyelitis optica spectrum disorder
ADAMTS13: a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13	LDH: lactate dehydrogenase
aHUS: atypical hemolytic uremic syndrome	MG-ADL: Myasthenia Gravis-Activities of Daily Living
AQP-4: aquaporin-4	MGFA: Myasthenia Gravis Foundation of America
EDSS: Expanded Disability Status Scale	PNH: paroxysmal nocturnal hemoglobinuria
FDA: Food and Drug Administration	STEC-HUS: Shiga toxin <i>E. coli</i> related hemolytic uremic syndrome
gMG: generalized myasthenia gravis	TMA: thrombotic microangiopathy
GPI: glycosylphosphatidylinositol	

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Corticosteroids		
betamethasone	Oral: 0.6 to 7.2 mg per day	7.2 mg/day
dexamethasone	Oral: 0.75 to 9 mg per day	9 mg/day
methylprednisolone	Oral: 12 to 20 mg per day; increase as needed by 4 mg every 2 to 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 to 3 days as needed	60 mg/day
Cholinesterase Inhibitors		
pyridostigmine (Mestinon [®] , Regonol [®])	Oral immediate-release: 600 mg daily in divided doses (range, 60-1500 mg daily in divided doses) Oral sustained release: 180-540 mg QD or BID IV or IM: 2 mg every 2-3 hours	See regimen
neostigmine (Bloxiverz [®])	Oral: 15 mg 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 QD 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 (nonmodified), 5 mg/kg/day in 2 divided doses	5 mg/kg/day
Rituxan [®] (rituximab), Riabni [™] (rituximab-	gMG	See regimen

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
arrx), 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	

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 is required for rituximab products

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 Soliris treatment outweigh the risks of developing a meningococcal infection
- Boxed warning(s): serious meningococcal infections

Appendix D: General Information

- Soliris 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 Soliris 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: <https://myasthenia.org/Portals/0/ADL.pdf>;
 - NMOSD: stabilization or reduction in EDSS total score. EDSS ranges from 0 (no disability) to 10 (death).
- 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.
- AQP-4: AQP-4-IgG-seropositive status is confirmed with the use of commercially available cell-binding kit assay (Euroimmun).
- Ultomiris is a humanized monoclonal antibody to complement component C5 that was engineered from Soliris. It is virtually identical to Soliris but has a longer half-life that allows for less frequent dosing intervals.
- Coverage is excluded for the following indications. The use of Soliris for these indications is considered investigational due to lack of conclusive, evidence-based data with randomized controlled trials. As such, alternative therapies for these indications include:
 - Antiphospholipid syndrome: anticoagulation therapy (e.g., vitamin K antagonists)
 - Unspecified nephritic syndrome with other morphologic changes: immunosuppression (e.g., prednisone, mycophenolate mofetil)

- In October 2021, the Institute for Clinical and Economic Review (ICER) published a final evidence report on the effectiveness and value of Soliris for the treatment of gMG. In adults with gMG positive for anti-AChR antibodies refractory to conventional therapy, there is:
 - Moderate certainty of a small or substantial net health benefit with high certainty of at least a small benefit for Soliris added to conventional therapy compared with conventional therapy alone (B+);
 - Insufficient evidence (I) to distinguish the net health benefits of rituximab from Soliris.
- The 2020 MGFA international consensus guidelines for gMG recommend that Soliris be considered after trials of other immunotherapies have been unsuccessful in meeting treatment goals. Soliris is a treatment option for severe, refractory, AChR antibody positive gMG.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
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 14 days	1,200 mg/dose

VI. Product Availability

Single-dose vial: 300 mg/30 mL

VII. References

1. Soliris Prescribing Information. New Haven, CT: Alexion Pharmaceuticals, Inc.; November 2020. Available at www.soliris.net. Accessed September 15, 2021.
2. Parker C, Omine M, Richards S, et al. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. *Blood* 2005; 106(12):3699-3709. doi:10.1182/blood-2005-04-1717.
3. Borowitz MJ, Craig FE, DiGiuseppe JA, et al. Guidelines for the diagnosis and monitoring of paroxysmal nocturnal hemoglobinuria and related disorders by flow cytometry. *Cytometry Part B (Clinical Cytometry)*. 2010; 78B: 211–230.
4. Loirat C, Fakhouri F, Ariceta G, et al. An international consensus approach to the management of atypical hemolytic uremic syndrome in children. *Pediatr Nephrol*. 2016; 31: 15-39.
5. Howard JF, 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, multicenter study. *Lancet Neurol*. 2017; 16(12): 976-986.
6. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidelines for the management of myasthenia gravis. *Neurology*. 2016; 87: 419-425.
7. Narayanaswami P, Sanders DB, Wolfe G, et al. International consensus guidance for management of myasthenia gravis: 2020 update. *Neurology*. 2021; 96: 114-122.
8. Muppidi S. The myasthenia gravis-specific activities of daily living profile. *Ann N Y Acad Sci*. 2012; 1274:114-119.
9. Pittock S.J et al. Eculizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. *NEJM* May 2019, DOI:10.1056.
10. Canaud G, Kamar N, Anglicheau D, et al. Eculizumab improves posttransplant thrombotic microangiopathy due to antiphospholipid syndrome recurrence but fails to prevent chronic vascular changes. *Am J Transplant*. 2013;13(8):2179-2185.
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12. Sellner J, Boggild M, Clanet M, et al. EFNS guidelines on diagnosis and management of neuromyelitis optica. *European Journal of Neurology*. 2010; 17: 1019–1032.

13. Institute for Clinical and Economic Review. Eculizumab and efgartigimod for the treatment of myasthenia gravis: effectiveness and value: Effectiveness and value (final report). Published October 20, 2021. Available at: <https://icer.org/assessment/myasthenia-gravis>. Accessed October 27, 2021.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q18 annual review: Added generalized myasthenia gravis indication and criteria for approval. PNH: Removed conditions constituting severe PNH that are not objective/specific. Modified requirement for 4 transfusions in last 12 months to 1 transfusion in the last 24 months per the inclusion criteria of the second pivotal trial for approval. aHUS: Added age requirements per prescribing information. Removed requirement for specific clinical presentation as a specialist is required to be involved in the care. Removed requirement for causes of aHUS to be ruled out as this is non-specific and under the purview of the provider. Both: Added nephrologist as a prescriber option for aHUS. Removed contraindication for Neisseria meningitidis infection and criteria surrounding meningococcal vaccination as these are covered by the Soliris REMS program. Reduced continued approval duration from 12 months to 6 months. Added STEC-HUS as an indication not covered.	12.12.17	02.18
1Q 2019 annual review: no significant changes; references reviewed and updated.	10.12.18	02.19
Aligned criteria with Ultomiris policy for PNH: allowed documentation of detectable GPI-deficient hematopoietic clones for flow cytometry; specified examples of positive response to therapy in Section II.A; references reviewed and updated.	02.19.19	05.19
Criteria added for new FDA indication: neuromyelitis optica spectrum disorder; references reviewed and updated.	08.13.19	11.19
1Q 2020 annual review: aHUS initial criteria and PNH/aHUS continued criteria updated to align with Ultomiris criteria; added antiphospholipid syndrome and unspecified nephritic syndrome with other morphologic changes to Section III diagnoses not covered; references reviewed and updated.	10.27.19	02.20
For NMOSD: added requirement against concurrent use with rituximab, Enspryng, or Uplizna.	07.29.20	11.20
1Q 2021 annual review: for PNH and aHUS, added requirement against concurrent use with Ultomiris; for NMOSD, added requirement for trial of rituximab; references reviewed and updated.	10.20.20	02.21
1Q 2022 annual review: no significant changes; for PNH, added restriction against concomitant use of Empaveli with Soliris with an exception for the initial 4-week cross-titration phase to align with previously approved approach for Empaveli; for NMOSD, specified that Ruxience is the preferred rituximab product; references reviewed and updated.	09.15.21	02.22

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.

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