Clinical Policy: Eculizumab (Soliris), Eculizumab-aeeb (Bkemv), Eculizumab-aagh (Epysqli)

Reference Number: PA.CP.PHAR.97
Effective Date: 01/2018
Last Review Date: 12/2024

Description
Eculizumab (Soliris®) and its biosimilar, eculizumab-aeeb (Bkemv™) and eculizumab-aagh (Epysqli®), are complement inhibitor.

FDA Approved Indication(s)
Soliris, Bkemv, and Epysqli are 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)

Soliris and Epysqli are additionally indicated for the treatment of:
- Adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AchR) antibody positive

Soliris is additionally indicated for the treatment of:
- Adult patients with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody positive.

Limitation(s) of use: Soliris, Bkemv, and Epysqli are not indicated for the treatment of patients with Shiga toxin *E. coli* related hemolytic uremic syndrome (STEC-HUS).

Policy/Criteria
It is the policy of PA Health & Wellness that Soliris, Bkemv, and Epysqli are **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 ≥ 18 years;
4. Flow cytometry shows detectable glycosylphosphatidylinositol (GPI)-deficient hematopoietic clones or ≥ 10% PNH cells;
5. Member meets one of the following (a or b):
   a. History of ≥ 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/Bkemv/Epysqli is not prescribed concurrently with Empaveli™, Fabhalta® or Ultomiris®, unless the member is in a 4-week period of cross-titration between Soliris/Bkemv/Epysqli 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 ≥ 2 months;
4. Member has signs of TMA as evidenced by all of the following (a, b, and c):
   a. Platelet count ≤ 150 x 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 or b):
   a. A disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13 (ADAMTS13) deficiency;
   b. STEC-HUS;
6. Soliris/Bkemv/Epysqli 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 in consultation with a neurologist;
3. Age ≥ 18 years;
4. Myasthenia Gravis-Activities of Daily Living (MG-ADL) score of 6 or more 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 at least one immunosuppressive therapies (*see Appendix B*) unless clinically significant adverse effects are experienced or all are contraindicated;
10. Soliris/Epysqli is not prescribed concurrently with Rystiggo®, Ultomiris, Vyvgart®, Vyvgart® Hytrulo, or Zilbrysq®;
11. 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 in consultation with a neurologist;
3. Age ≥ 18 years;

4. Member has positive serologic test for anti-AQP4 antibodies;
5. 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, with at least one relapse occurring in the last 12 months;
6. Baseline expanded disability status scale (EDSS) score of ≤ 7;
7. Failure of rituximab* (Ruxience and Truxima are preferred) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization may be required for rituximab*
8. Soliris is not prescribed concurrently with rituximab, Enspryng®, Uplizna®, or Ultomiris;
9. 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: Refer to PA.CP.PMN.53

II. Continued Approval

A. Paroxysmal nocturnal hemoglobinuria and Atypical hemolytic uremic syndrome (must meet all)**:**

1. Currently receiving medication via PA Health & Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care Policy (PA.PHARM.01) applies;
2. Member is responding positively to therapy as evidenced by, including but not limited to, improvement in any of the following parameters (a or b):
   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. Reuced need for dialysis;
3. Soliris/Bkemv/Epysqli is not prescribed concurrently with (a or b):
   a. PNH: Empaveli, Fabhalta, 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 PA Health & Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care Policy (PA.PHARM.01) applies;
2. Member is responding positively to therapy as evidenced by a 2-point reduction from baseline in MG-ADL total score;
3. Soliris/Epysqli is not prescribed concurrently with Rystiggo, Ultomiris, Vyvgart, Vyvgart Hytrulo, or Zilbrysq;
4. 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 PA Health & Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care Policy (PA.PHARM.01) applies;
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;
   b. EDSS;
   c. Visual acuity;
3. Soliris is not prescribed concurrently with rituximab, Enspryng, Uplizna or Ultomiris;
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 PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care Policy (PA.PHARM.01) applies; or
2. Refer to PA.CP.PMN.53

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 policies – PA.CP.PMN.53
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: acetylcholine receptor
ADAMTS13: a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13
aHUS: atypical hemolytic uremic syndrome
AQP-4: aquaporin-4
EDSS: Expanded Disability Status Scale
FDA: Food and Drug Administration

gMG: generalized myasthenia gravis
GPI: glycosylphosphatidylinositol
LDH: lactate dehydrogenase
MG-ADL: Myasthenia Gravis-Activities of Daily Living
MGFA: Myasthenia Gravis Foundation of America
PNH: paroxysmal nocturnal hemoglobinuria
STEC-HUS: Shiga toxin E. coli related hemolytic uremic syndrome
TMA: thrombotic microangiopathy

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 PO per day	7.2 mg/day
dexamethasone	Oral: 0.75 to 9 mg/day PO	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. Maximum: 60 mg/day	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 (Non-modified), 5 mg/kg/day in 2 divided doses	5 mg/kg/day
Rituxan® (rituximab), Riabni™ (rituximab-arrx), Ruxience™	**gMG** 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**	See regimen

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
(rituximab-pvvr), Truxima® (rituximab-abbs)*†	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
- Boxed warning(s): serious meningococcal infections

Appendix D: General Information

- Soliris/Bkemv/Epysqli 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/Bkemv/Epysqli 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.
- Aquaporin-4 (AQP-4): AQP-4-IgG-seroposotive 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/Bkemv 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

Drug Name	Indication	Dosing Regimen	Maximum Dose
Soliris, Bkemv, Epysqli	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
Soliris, Epysqli	gMG	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
Soliris	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

VI. Product Availability

Drug Name	Availability
Soliris	Single-dose vial: 300 mg/30 mL
Bkemv	Single-dose vial: 300 mg/30 mL
Epysqli	Single-dose vial: 300 mg/30 mL

VII. References

1. Soliris Prescribing Information. New Haven, CT: Alexion Pharmaceuticals, Inc.; March 2024. Available at: www.soliris.net. Accessed May 8, 2024.
2. Bkemv Prescribing Information. Thousand Oaks, CA: Amgen Inc.; May 2024. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761333s000lbl.pdf. Accessed May 29, 2024.
3. Epysqli Prescribing Information. Yeonsu-gu, Incheon: Samsung Bioepis Co., Ltd.; November 2024. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761340s003lbl.pdf. Accessed November 21, 2024.
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12. Muppidi S. The myasthenia gravis-specific activities of daily living profile. Ann N Y Acad Sci. 2012; 1274:114-119.
13. Pittock SJ, et al. Eculizumab in aquaporin-4-postive neuromyelitis optica spectrum disorder. NEJM. May 2019. DOI:10.1056.
14. 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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16. 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.
17. 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 November 3, 2022.

18. Kumpfel T, Giglhuber K, Aktas O, et al. Update on the diagnosis and treatment of neuromyelitis optica spectrum disorders (NMOSD) – revised recommendations of the Neuromyelitis Optica Study Group (NEMOS). Part II: Attack therapy and long-term management. Journal of Neurology. 2023; 271: 141-176.

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J1300	Injection, eculizumab 10 mg
Q5139	Injection, eculizumab-aeeb (bkemv), biosimilar, 10 mg

Reviews, Revisions, and Approvals	Date
Policy created	03/2017
For 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. For aHUS, removed requirements 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. For PNH and aHUS, removed contraindication for Neisseria meningitidis infection as this is covered by the REMS program. Added age requirements per prescribing information. Added nephrologist as a prescriber option for aHUS. Removed criteria surrounding meningococcal vaccination as this is covered by the Soliris REMS program. Added STEC-HUS as an indication not covered. Modified all approval durations to 6 months. Added generalized myasthenia gravis indication and criteria for approval. References reviewed and updated.	02/2018
2Q 2019 annual review: Added note to appendix B that prior authorization is required for Rituxan; 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.	04/2019
1Q 2020 annual review: aHUS initial criteria and PNH/aHUS continued criteria updated to align with Ultomiris criteria; Criteria added for new FDA indication: neuromyelitis optica spectrum disorder; references reviewed and updated.	01/2020
For NMOSD added redirection to rituximab product and added requirement against concurrent use with rituximab, Enspryng, or Uplizna; added antiphospholipid syndrome and unsp nephritic syndrome with other	10/2020

Reviews, Revisions, and Approvals	Date
morphologic changes to Section III diagnoses not covered; references reviewed and updated	
1Q 2021 annual review: for PNH and aHUS, added requirement against concurrent use with Ultomiris; for NMOSD, specified that Ruxience is the preferred rituximab product; references reviewed and updated.	01/2021
1Q 2022 annual review: 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 Truxima is also a preferred rituximab product; references reviewed and updated.	01/2022
Per February SDC and prior clinical guidance, for NMOSD added stepwise redirection requirement if member has failed rituximab, then member must use Enspryng.	04/2022
Per August SDC and prior clinical guidance, for NMOSD, removed redirection to Enspryng; for gMG modified from two to one immunosuppressive therapy required, added requirement that Soliris is not prescribed concurrently with Ultomiris or Vyvgart.	10/2022
1Q 2023 annual review: no significant changes; references reviewed and updated.	01/2023
3Q 2023 annual review: no significant changes; references reviewed and updated.	07/2023
3Q 2024 annual review: RT4: added newly approved biosimilar, Bkemv; updated the list of therapies that Soliris/Bkemv should not be prescribed concurrently with to include Rystiggo, Vyvgart Hytrulo, and Zilbrysq for gMG, Fabhalta for PNH, and Ultomiris for NMOSD; revised contraindications in Appendix C per updated Soliris prescribing information; references reviewed and updated.	07/2024
HCPCS code added [Q5139] and removed code [C9399] RT4: added newly approved biosimilar, Epysqli. RT4: updated FDA approved indication for Epysqli to include adult patients with gMG who are AChR antibody positive; for gMG continuation of therapy requests, extended continuity of care allowance to Bkemv and Epysqli; for NMOSD, clarified relapse requirements per PA ops request.	12/2024