| Reference number |
| --- |
| 3537-A |

# POLICY Document for SOLIRIS (eculizumab) BKEMV (eculizumab-aeeb) EPYSQLI (eculizumab-aagh)

The overall objective of this policy is to support the appropriate and cost-effective use of the medication, specific to use of preferred medication options, and overall, clinically appropriate use. This document provides specific information to both sections of the overall policy.

**Section 1: Preferred Product**
- Policy information specific to preferred medications

**Section 2: Site of Care**
- Policy information specific to site of care (outpatient, hospital outpatient, home infusion)

**Section 3: Clinical Criteria**
- Policy information specific to the clinical appropriateness for the medication

## Section 1: Preferred Product

### CAREFIRST: EXCEPTIONS CRITERIA
### COMPLEMENT INHIBITORS

### PREFERRED PRODUCTS: ULTOMIRIS, VYVGART, VYVGART HYTRULO

**Client Requested:** The intent of the criteria is to ensure that patients follow selection elements as established by CareFirst.

**POLICY**
This policy informs prescribers of preferred products and provides an exception process for targeted products through prior authorization.

**I. PLAN DESIGN SUMMARY**

This program applies to the Complement inhibitor products specified in this policy. Coverage for targeted products is provided based on clinical circumstances that would exclude the use of the preferred product and may be based on previous use of a product. The coverage review process will ascertain situations where a clinical exception can be made. This program applies to all members requesting treatment with a targeted product.

Each referral is reviewed based on all utilization management (UM) programs implemented for the client.

**Table. Complement Inhibitor Products**

| | Product(s) |
| --- | --- |
| **Preferred*** | • **Ultomiris** (ravulizumab-cwvz)<br>• **Vyvgart** (efgartigimod alfa)<br>• **Vyvgart** Hytrulo (efgartigimod alfa and hyaluronidase) |
| **Targeted** | • **Empaveli** (pegcetacoplan)<br>• **Enspryng** (atralizumab-mwge)<br>• **Piasky** (crovalimab)<br>• **Rystiggo** (rozanolixizumab)<br>• **Soliris** (eculizumab)<br>• **Uplizna** (inebilizumab-cdon) |

*: Medications considered formulary or preferred on your plan may still require a clinical prior authorization review.

**II. EXCEPTION CRITERIA**

This program applies to members requesting treatment for an indication that is FDA-approved for the preferred product.

For Myasthenia Gravis, coverage for the targeted product is provided when member has a documented inadequate response, contraindication, or intolerable adverse event to all the preferred products.

For all other indications, coverage for the targeted product is provided when member has a documented inadequate response, contraindication, or intolerable adverse event to Ultomiris.

# Section 2: Site of Care

# CareFirst Site of Care Criteria
# Administration of Intravenous Eculizumab
# Bkemv, Epysqli, Soliris

# POLICY

**I. CRITERIA FOR APPROVAL FOR ADMINISTRATION IN OUTPATIENT HOSPITAL SETTING**

This policy provides coverage for administration of eculizumab in an outpatient hospital setting for 12 days (2 doses) when a member is new to therapy or is reinitiating therapy after not being on therapy for at least 6 months.

This policy provides coverage for administration of eculizumab in an outpatient hospital setting for a longer

course of treatment when ANY of the following criteria are met:

A. The member has experienced an adverse reaction to the medication that did not respond to conventional interventions (eg, acetaminophen, steroids, diphenhydramine, fluids, other pre-medications or slowing of the infusion rate) or a severe adverse event (anaphylaxis, anaphylactoid reactions, myocardial infarction, thromboembolism, or seizures) during or immediately after an infusion.
B. The member is medically unstable (eg respiratory, cardiovascular, or renal conditions).
C. The member has severe venous access issues that require the use of special interventions only available in the outpatient hospital setting.
D. The member has significant behavioral issues and/or physical or cognitive impairment that would impact the safety of the infusion therapy AND the patient does not have access to a caregiver.
E. Alternative infusion sites (pharmacy, physician office, ambulatory care, etc.) are greater than 30 miles from the member's home.
F. The member is less than 14 years of age.

For situations where administration of eculizumab does not meet the criteria for outpatient hospital infusion, coverage for eculizumab is provided when administered in alternative sites such as; physician office, home infusion or ambulatory care.

**REQUIRED DOCUMENTATION**

The following information is necessary to initiate the site of care prior authorization review (where applicable):

G. Medical records supporting the member has experienced an adverse reaction that did not respond to conventional interventions or a severe adverse event during or immediately after an infusion
H. Medical records supporting the member is medically unstable
I. Medical records supporting the member has severe venous access issues that require specialized interventions only available in the outpatient hospital setting
J. Medical records supporting the member has behavioral issues and/or physical or cognitive impairment and no access to a caregiver
K. Records supporting alternative infusion sites are greater than 30 miles from the member's home.
L. Medical records supporting the member is new to therapy

# Section 3: Clinical Criteria

## SPECIALTY GUIDELINE MANAGEMENT

### SOLIRIS (eculizumab)
### BKEMV (eculizumab-aeeb)
### EPYSQLI (eculizumab-aagh)

**POLICY**

**I. INDICATIONS**

The indications below including FDA-approved indications and compendial uses are considered covered benefits provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications
Soliris is indicated for the treatment of:
A. Paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis
B. Atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy
C. Generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AchR) antibody positive
D. Neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive

Bkemv and Epysqli are indicated for the treatment of:
A. Paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis
B. Atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy

*Limitations 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).*

All other indications are considered experimental/investigational and not medically necessary.

## II. DOCUMENTATION

Submission of the following information is necessary to initiate the prior authorization review:
A. For initial requests:
    1. Atypical hemolytic uremic syndrome: ADAMTS 13 level
    2. Paroxysmal nocturnal hemoglobinuria: Flow cytometry used to show results of glycosylphosphatidylinositol-anchored proteins (GPI-APs) deficiency
    3. Generalized myasthenia gravis:
        i. Positive anti-acetylcholine receptor (AChR) antibody test
        ii. Myasthenia Gravis Foundation of America (MGFA) clinical classification
        iii. MG activities of daily living score
        iv. Previous medications tried, including response to therapy. If therapy is not advisable, documentation of clinical reasons to avoid therapy.
    4. Neuromyelitis optica spectrum disorder: Immunoassay used to confirm anti-aquaporin-4 (AQP4) antibody is present
B. For continuation requests: Chart notes or medical record documentation supporting positive clinical response.

## III. CRITERIA FOR INITIAL APPROVAL

**A. Atypical hemolytic uremic syndrome**
Authorization of 6 months may be granted for treatment of atypical hemolytic uremic syndrome (aHUS) not caused by Shiga toxin when all of the following criteria are met:
1. ADAMTS 13 activity level above 5%

2. Absence of Shiga toxin
3. The requested medication will not be used in combination with another complement inhibitor (e.g., Ultomiris) for the treatment of aHUS.

**B. Paroxysmal nocturnal hemoglobinuria**

Authorization of 6 months may be granted for treatment of paroxysmal nocturnal hemoglobinuria (PNH) when all of the following criteria are met:

1. The diagnosis of PNH was confirmed by detecting a deficiency of glycosylphosphatidylinositol-anchored proteins (GPI-APs) (e.g., at least 5% PNH cells, at least 51% of GPI-AP deficient poly-morphonuclear cells)
2. Flow cytometry is used to demonstrate GPI-APs deficiency
3. Member has and exhibits clinical manifestations of disease (e.g., LDH > 1.5 ULN, thrombosis, renal dysfunction, pulmonary hypertension, dysphagia)
4. The requested medication will not be used in combination with another complement inhibitor (e.g., Empaveli, Fabhalta, Piasky, Ultomiris) for the treatment of PNH (concomitant use with Voydeya is allowed).

**C. Generalized myasthenia gravis**

Authorization of 6 months may be granted for treatment of generalized myasthenia gravis (gMG) when all of the following criteria are met:

1. Anti-acetylcholine receptor (AchR) antibody positive
2. Myasthenia Gravis Foundation of America (MGFA) clinical classification II to IV
3. MG activities of daily living (MG-ADL) total score of greater than or equal to 5
4. Meets one of the following:
    i. Member has had an inadequate response or intolerable adverse event to at least two immunosuppressive therapies over the course of at least 12 months (e.g., azathioprine, corticosteroids, cyclosporine, methotrexate, mycophenolate, tacrolimus)
    ii. Member has had an inadequate response or intolerable adverse event to at least one immunosuppressive therapy and intravenous immunoglobulin (IVIG) over the course of at least 12 months
    iii. Member has a documented clinical reason to avoid therapy with immunosuppressive agents and IVIG
5. The requested medication will not be used in combination with another complement inhibitor (e.g., Ultomiris, Zilbrysq) or neonatal Fc receptor blocker (e.g., Vyvgart, Vyvgart Hytrulo, Rystiggo).

**D. Neuromyelitis optica spectrum disorder**

Authorization of 6 months may be granted for treatment of neuromyelitis optica spectrum disorder (NMOSD) when all of the following criteria are met:

1. Anti-aquaporin-4 (AQP4) antibody positive
2. Member exhibits one of the following core clinical characteristics of NMOSD:
    i. Optic neuritis
    ii. Acute myelitis
    iii. Area postrema syndrome (episode of otherwise unexplained hiccups or nausea and vomiting)
    iv. Acute brainstem syndrome
    v. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
    vi. Symptomatic cerebral syndrome with NMOSD-typical brain lesions
3. The member will not receive the requested medication concomitantly with other biologics for the treatment of NMOSD.

## IV. CONTINUATION OF THERAPY

### A. Atypical hemolytic uremic syndrome

Authorization of 12 months may be granted for continued treatment in members requesting reauthorization when all of the following criteria are met:

1. There is no evidence of unacceptable toxicity or disease progression while on the current regimen.
2. The member demonstrates a positive response to therapy (e.g., normalization of lactate dehydrogenase (LDH) levels, platelet counts).
3. The requested medication will not be used in combination with another complement inhibitor (e.g., Ultomiris) for the treatment of aHUS.

### B. Paroxysmal nocturnal hemoglobinuria

Authorization of 12 months may be granted for continued treatment in members requesting reauthorization when all of the following criteria are met:

1. There is no evidence of unacceptable toxicity or disease progression while on the current regimen.
2. The member demonstrates a positive response to therapy (e.g., improvement in hemoglobin levels, normalization of lactate dehydrogenase [LDH] levels).
3. The requested medication will not be used in combination with another complement inhibitor (e.g., Empaveli, Fabhalta, Piasky, Ultomiris) for the treatment of PNH (concomitant use with Voydeya is allowed).

### C. Generalized myasthenia gravis

Authorization of 12 months may be granted for continued treatment in members requesting reauthorization when all of the following criteria are met:

1. There is no evidence of unacceptable toxicity or disease progression while on the current regimen.
2. The member demonstrates a positive response to therapy (e.g., improvement in MG-ADL score, MG Manual Muscle Test (MMT), MG Composite).
3. The requested medication will not be used in combination with another complement inhibitor (e.g., Ultomiris, Zilbrysq) or neonatal Fc receptor blocker (e.g., Vyvgart, Vyvgart Hytrulo, Rystiggo).

### D. Neuromyelitis optica spectrum disorder

Authorization of 12 months may be granted for continued treatment in members requesting reauthorization when all of the following criteria are met:

1. There is no evidence of unacceptable toxicity or disease progression while on the current regimen.
2. The member demonstrates a positive response to therapy (e.g., reduction in number of relapses).
3. The member will not receive the requested medication concomitantly with other biologics for the treatment of NMOSD.

## V. DOSAGE AND ADMINISTRATION

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

## REFERENCES

### SECTION 1

1. Empaveli [package insert]. Waltham, MA: Apellis Pharmaceuticals, Inc; February 2024.

2. Enspryng [package insert]. San Francisco, CA: Genentech, Inc.; March 2022.
3. Piasky [package insert]. South San Francisco, CA: Genetech Inc; June 2024.
4. Rystiggo [package insert]. Smyrna, GA: UCB, Inc; June 2023.
5. Soliris [package insert]. Boston, MA: Alexion Pharmaceuticals Inc; September 2024.
6. Ultomiris [package insert]. Boston, MA: Alexion Pharmaceuticals Inc; September 2024.
7. Uplinza [package insert]. Deerfield, IL: Horizon Therapeutics; July 2021.
8. Vyvgart [package insert]. Boston, MA: argenx US, Inc; August 2024
9. Vyvgart Hytrulo [package insert]. Boston, MA: argenx US, Inc; August 2024

**SECTION 2**

1. Soliris [package insert]. New Haven, CT: Alexion Pharmaceuticals Inc; March 2024.
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. 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.
4. Bkemv [package insert]. Thousand Oaks, CA: Amgen Inc.; May 2024.
5. Epysqli [package insert]. Republic of Korea: Samsung Bioepis Co., Ltd.; July 2024.

**SECTION 3**

1. Soliris [package insert]. Boston, MA: Alexion Pharmaceuticals, Inc.; March 2024.
2. Loirat C, Fakhouri F, Ariceta G, et al. An international consensus approach to the management of atypical hemolytic uremic syndrome in children. *Pediatr Nephrol*. Published online: April 11, 2015.
3. Parker CJ. Management of paroxysmal nocturnal hemoglobinuria in the era of complement inhibitory therapy. *Hematology.* 2011; 21-29.
4. Sanders D, Wolfe G, Benatar M et al. International consensus guidance for management of myasthenia gravis. *Neurology*. 2021; 96 (3) 114-122 .
5. Jaretzki A, Barohn RJ, Ernstoff RM et al. Myasthenia Gravis: Recommendations for Clinical Research Standards. *Ann Thorac Surg*. 2000;70: 327-34.
6. Hillmen P, Young NS, Schubert J, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. *NEJM.* 2006;335:1233-43.
7. Howard JF, Utsugisawa K, Benatar M. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalized myasthenia gravis (REGAIN); a phase 3, randomized, double-blind, placebo-controlled, multicenter study. *Lancet Neurol*. 2017 Oct 20. http://dx.doi.org/10.1016/S1474-4422(17)30369-1Ingenix HCPCS Level II, Expert 2011.
8. 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.
9. Borowitz MJ, Craig F, DiGiuseppe JA, et al. Guidelines for the Diagnosis and Monitoring of Paroxysmal Nocturnal Hemoglobinuria and Related Disorders by Flow Cytometry. *Cytometry B Clin Cytom*. 2010: 78: 211-230.
10. Preis M, Lowrey CH. Laboratory tests for paroxysmal nocturnal hemoglobinuria (PNH). Am J Hematol. 2014;89(3):339-341.
11. Lee JW, Sicre de Fontbrune F, Wong LL, et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: The 301 study. Blood. 2018 Dec 3; pii: blood-2018-09-876136.
12. Pittock SJ, Berthele A, Kim HJ, et al. Eculizumab in Aquaporin-4-Positive Neuromyelitis Optica Spectrum Disorder. *N Engl J Med*. 2019 May 3. doi: 10.1056/NEJMoA1900866.

13. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology.* 2015; 85:177-189.
14. Parker CJ. Update on the diagnosis and management of paroxysmal nocturnal hemoglobinuria. Hematology Am Soc Hematol Educ Program. 2016;2016(1):208-216.
15. Dezern AE, Borowitz MJ. ICCS/ESCCA consensus guidelines to detect GPI-deficient cells in paroxysmal nocturnal hemoglobinuria (PNH) and related disorders part 1 - clinical utility. Cytometry B Clin Cytom. 2018 Jan;94(1):16-22.
16. Barnett C, Herbelin L, Dimachkie MM, Barohn RJ. Measuring Clinical Treatment Response in Myasthenia Gravis. Neurol Clin. 2018 May;36(2):339-353.
17. Bkemv [package insert]. Thousand Oaks, CA: Amgen Inc.; May 2024.
18. Epysqli [package insert]. Republic of Korea: Samsung Bioepis Co., Ltd.; July 2024.