Corporate Medical Policy: Complement C5 Inhibitors **"Notification"** **POLICY EFFECTIVE JANUARY 1, 2026**

Restricted Product(s):

- crovalimab-akkz (PiaSky®) intravenous infusion and subcutaneous injection for administration by a healthcare professional
- eculizumab (Soliris®) intravenous infusion for administration by a healthcare professional
- eculizumab-aeeb (Bkemv®) intravenous infusion for administration by a healthcare professional
- eculizumab-aagh (Epysqli®) intravenous infusion for administration by a healthcare professional
- ravulizumab-cwvz (Ultomiris®) intravenous infusion for administration by a healthcare professional

FDA Approved Use:

- Crovalimab-akkz (PiaSky®)
  - For the treatment of adult and pediatric patients 13 years and older with paroxysmal nocturnal hemoglobinuria (PNH) and body weight of at least 40 kg

- Eculizumab (Soliris®), Eculizumab-aeeb (Bkemv®), Eculizumab-aagh (Epysqli®)
  - For the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis
  - For the treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy
    - Limitation of use: Not for the treatment of Shiga toxin E. coli related hemolytic uremic syndrome
  - For the treatment of adult and pediatric patients 6 years of age and older with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody positive
  - For the treatment of adults with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody positive

- Ravulizumab-cwvz (Ultomiris®)
  - For the treatment of adults and pediatric patients one month of age and older with paroxysmal nocturnal hemoglobinuria (PNH)
  - For 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)
    - Limitation of use: Not for the treatment of Shiga toxin E. coli related hemolytic uremic syndrome
  - For the treatment of adults with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody-positive
  - For the treatment of adults with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody-positive

Criteria for Medical Necessity:

The restricted product(s) may be considered medically necessary when the following criteria are met:

Initial Criteria for Approval:

1. The patient has a diagnosis of **paroxysmal nocturnal hemoglobinuria (PNH) [medical record documentation required]**; **AND**
    a. ONE of the following:
        i. If the request is for crovalimab (PiaSky), the patient is 13 years of age or older and weighs at least 40 kg **[medical record documentation required]**; **OR**
        ii. If the request is for an eculizumab product (i.e., Soliris, Bkemv, or Epysqli), the patient is 18 years of age or older; **OR**
        iii. If the request is for ravulizumab (Ultomiris), the patient is 1 month of age or older; **AND**
    b. The diagnosis has been confirmed by ALL of the following:
        i. Flow cytometry with at least 2 independent flow cytometry reagents on at least 2 cell lineages (e.g., red blood cells [RBCs] and white blood cells [WBCs]) demonstrating that the patient's peripheral blood cells are deficient in glycosylphosphatidylinositol-anchored proteins (GPI-APs) **[medical record documentation required]**; **AND**
        ii. Laboratory results showing a lactate dehydrogenase (LDH) level ≥ 1.5 times the upper limit of normal at baseline prior to starting complement inhibitor therapy **[medical record documentation required]**; **AND**
        iii. The patient has had at least one PNH-related sign or symptom in the past 3 months prior to starting complement inhibitor therapy (e.g., fatigue, hemoglobinuria, abdominal pain, dyspnea, anemia [hemoglobin < 10 g/dL], history of a major adverse vascular event [including thrombosis], dysphagia, erectile dysfunction, or history of RBC transfusion due to PNH) **[medical record documentation required]**; **AND**
    c. ONE of the following:
        i. The request is for ravulizumab (Ultomiris); **OR**
        ii. The request is for crovalimab (PiaSky) AND ONE of the following:
            1. The patient is 13 to less than 18 years of age; **AND**
                a. The patient has tried and had an inadequate response to ravulizumab (Ultomiris) **[medical record documentation required]**; **OR**
                b. The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to ravulizumab (Ultomiris) **[medical record documentation required]**; **OR**
            2. The patient is 18 years of age or older; **AND**
                a. The patient has tried and had an inadequate response to TWO of the following: iptacopan (Fabhalta), pegcetacoplan (Empaveli), ravulizumab (Ultomiris) **[medical record documentation required]**; **OR**
                b. The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to ALL of the following: iptacopan (Fabhalta), pegcetacoplan (Empaveli), AND ravulizumab (Ultomiris) **[medical record documentation required]**; **OR**

iii. The request is for an eculizumab product (i.e., Soliris, Bkemv, or Epysqli) AND ONE of the following:
1. The patient has tried and had an inadequate response to ALL of the following: iptacopan (Fabhalta), pegcetacoplan (Empaveli), AND ravulizumab (Ultomiris) **[medical record documentation required]**; **OR**
2. The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to ALL of the following: iptacopan (Fabhalta), pegcetacoplan (Empaveli), AND ravulizumab (Ultomiris) **[medical record documentation required]**; **OR**

2. The patient has a diagnosis of **atypical hemolytic uremic syndrome (aHUS) [medical record documentation required]**; **AND**
   a. ONE for the following:
      i. If the request is for an eculizumab product (i.e., Soliris, Bkemv, or Epysqli), the patient is 2 months of age or older; **OR**
      ii. If the request is for ravulizumab (Ultomiris), the patient is 1 month of age or older; **AND**
   b. A differential diagnosis of complement-mediated HUS has been demonstrated (i.e., screening for Shiga toxin-producing *E. coli* [STEC] for STEC-HUS, pneumococcal culture of blood/sputum/cerebrospinal or pleural fluid for pneumococcal-associated HUS, ADAMTS13 less than 10% activity for thrombotic thrombocytopenic purpura [TTP], screening for defective cobalamin metabolism) **[medical record documentation required]**; **AND**
   c. The patient has an ADAMTS13 activity level greater than 5% **[medical record documentation required]**; **AND**
   d. The patient does NOT have Shiga toxin *E.coli* related hemolytic uremic syndrome (STEC-HUS) **[medical record documentation required]**; **AND**
   e. ONE of the following:
      i. The request is for ravulizumab (Ultomiris); **OR**
      ii. The request is for an eculizumab product (i.e., Soliris, Bkemv, or Epysqli) AND ONE of the following:
         1. The patient has tried and had an inadequate response to ravulizumab (Ultomiris) **[medical record documentation required]**; **OR**
         2. The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to ravulizumab (Ultomiris) **[medical record documentation required]**; **OR**

3. The patient has a diagnosis of **generalized myasthenia gravis (gMG) [medical record documentation required]**; **AND**
   a. The request is for an eculizumab product (i.e., Soliris, Bkemv, or Epysqli) or ravulizumab (Ultomiris); **AND**
   b. ONE of the following:
      i. The patient is 18 years of age or older; **OR**
      ii. If the request is for an eculizumab product (i.e., Soliris, Bkemv, or Epysqli), the patient is 6 years of age or older; **AND**
   c. The patient has a positive serological test for anti-acetylcholine receptor (AChR) antibodies **[medical record documentation required]**; **AND**
   d. The patient has a Myasthenia Gravis Foundation of America (MGFA) clinical classification class of II to IVb, or as scored by a comparable standardized rating scale that reliably measures MG disease severity **[medical record documentation required]**; **AND**

e. The patient has impaired activities of daily living defined by a Myasthenia Gravis Activities of Daily Living (MG-ADL) total score of 6 or higher, or as scored by a comparable standardized rating scale that reliably measures MG disease severity **[medical record documentation required]**; **AND**
f. ONE of the following:
    i. The prescriber has assessed the patient's current medications and discontinued any medications known to exacerbate myasthenia gravis (e.g., beta blockers, procainamide, quinidine, magnesium, anti-programmed death receptor-1 monoclonal antibodies, hydroxychloroquine, aminoglycosides) **[medical record documentation required]**; **OR**
    ii. The prescriber has provided clinical rationale indicating that discontinuation of the offending agent is not clinically appropriate **[medical record documentation required]**; **AND**
g. ONE of the following:
    i. The patient has tried and had an inadequate response to at least ONE conventional agent used for the treatment of myasthenia gravis for at least 12 months (i.e., corticosteroids, azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, methotrexate, cyclophosphamide) **[medical record documentation required]**; **OR**
    ii. The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to ALL conventional agents used for the treatment of myasthenia gravis (i.e., corticosteroids, azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, methotrexate, cyclophosphamide) **[medical record documentation required]**; **OR**
    iii. The patient required chronic intravenous immunoglobulin (IVIG) (i.e., at least every 3 months over 12 months without symptom control) **[medical record documentation required]**; **OR**
    iv. The patient required chronic plasmapheresis/plasma exchange (i.e., at least every 3 months over 12 months without symptom control) **[medical record documentation required]**; **AND**
h. ONE of the following:
    i. The request is for ravulizumab (Ultomiris); **OR**
    ii. The request is for an eculizumab product (i.e., Soliris, Bkemv, or Epysqli) AND the patient is 18 years of age or older; **AND**
        1. ONE of the following:
            a. The patient has tried and had an inadequate response to ALL of the following: ravulizumab (Ultomiris), rozanolixizumab (Rystiggo), AND efgartigimod (Vyvgart, Vyvgart Hytrulo) **[medical record documentation required]**; **OR**
            b. The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to ALL of the following: ravulizumab (Ultomiris), rozanolixizumab (Rystiggo), AND efgartigimod (Vyvgart, Vyvgart Hytrulo) **[medical record documentation required]**; **OR**

4. The patient has a diagnosis of **neuromyelitis optica spectrum disorder (NMOSD) [medical record documentation required]**; **AND**
    a. The request is for an eculizumab product (i.e., Soliris, Bkemv, or Epysqli) or ravulizumab (Ultomiris); **AND**
    b. The patient is 18 years of age or older; **AND**

c. The patient is anti-aquaporin-4 (AQP4) antibody seropositive **[medical record documentation required]**; **AND**
d. The diagnosis has been confirmed by the presence of at least ONE of the following core clinical characteristics **[medical record documentation required]**:
    i. Optic neuritis; **OR**
    ii. Acute myelitis; **OR**
    iii. Area postrema syndrome: Episode of otherwise unexplained hiccups or nausea and vomiting; **OR**
    iv. Acute brainstem syndrome; **OR**
    v. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions; **OR**
    vi. Symptomatic cerebral syndrome with NMOSD-typical brain lesions; **AND**
e. The patient has had at least ONE attack or relapse in the last 12 months prior to treatment with an immunotherapy or complement inhibitor for NMOSD (e.g., an eculizumab product, inebilizumab, ravulizumab, a rituximab product, satralizumab, etc.) **[medical record documentation required]**; **AND**
f. The patient does NOT have any other alternative diagnoses to explain or cause the current disease symptoms (e.g., multiple sclerosis, ischemic optic neuropathy, etc.) **[medical record documentation required]**; **AND**
g. ONE of the following:
    i. The request is for ravulizumab (Ultomiris); **OR**
    ii. The request is for an eculizumab product (i.e., Soliris, Bkemv, or Epysqli) AND ONE of the following:
        1. The patient has tried and had an inadequate response to ALL of the following: inebilizumab (Uplizna), ravulizumab (Ultomiris), AND satralizumab (Enspryng) **[medical record documentation required]**; **OR**
        2. The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to ALL of the following: inebilizumab (Uplizna), ravulizumab (Ultomiris), AND satralizumab (Enspryng) **[medical record documentation required]**; **AND**

5. If the request is for Soliris (eculizumab) or a non-preferred eculizumab biosimilar product (e.g., eculizumab-aeeb [Bkemv], etc.), ONE of the following:
    a. The patient has tried and had an inadequate response to the following preferred eculizumab biosimilar product: eculizumab-aagh (Epysqli) **[medical record documentation required]**; **OR**
    b. The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to eculizumab-aagh (Epysqli) that is NOT expected to occur with the requested product **[medical record documentation required]**; **OR**
    c. The patient has a documented serious adverse event that required medical intervention to eculizumab-aagh (Epysqli) that is NOT anticipated with the requested product **[medical record documentation required]**; **AND**
        i. The prescriber has completed and submitted an FDA MedWatch Adverse Event Reporting Form **[medical record documentation required]**; **AND**

6. The patient will NOT be using the requested agent in combination with another agent used to treat the requested indication (**see Combination Agents table below) **[medical record documentation required]**; **AND**
7. The prescriber is a specialist in the area of the patient's diagnosis (e.g., hematologist, neurologist) or has consulted with a specialist in the area of the patient's diagnosis **[medical record documentation required]**; **AND**
8. The requested quantity does NOT exceed the maximum units allowed for the duration of approval (see table below); **AND**
9. For requests for injection or infusion administration of the requested medication in an **inpatient or outpatient hospital setting,** Site of Care Criteria applies (outlined below)*

Duration of Approval: 180 days (6 months)

Continuation Criteria for Approval:

1. The patient was approved through Blue Cross NC initial criteria for approval; **OR**
2. The patient would have met initial criteria for approval at the time they started therapy **[medical record documentation required]**; **AND**
3. For patients with a diagnosis of **paroxysmal nocturnal hemoglobinuria (PNH)**:
    a. The patient has had either stabilization or improvement of symptoms from baseline while using the requested agent (e.g., significant reduction in RBC transfusion requirements, stabilization/improvement of hemoglobin, reduction of LDH, no thromboembolism events persisting while using the requested agent, stabilization/improvement of symptoms) **[medical record documentation required]**; **OR**
4. For patients with a diagnosis of **atypical hemolytic uremic syndrome (aHUS)**:
    a. The request is for an eculizumab product (i.e., Soliris, Bkemv, or Epysqli) or ravulizumab (Ultomiris); **AND**
    b. The patient has demonstrated a positive clinical response while using the requested agent as measured by hematological parameters or thrombotic microangiopathy (TMA) response (e.g., improved platelet count, reduction of LDH, stabilization/improvement of renal function) **[medical record documentation required]**; **OR**
5. For patients with a diagnosis of **generalized myasthenia gravis (gMG)**:
    a. The request is for an eculizumab product (i.e., Soliris, Bkemv, or Epysqli) or ravulizumab (Ultomiris); **AND**
    b. The patient has demonstrated a positive clinical response while using the requested agent (e.g., improved MG-ADL total score, improved quantitative myasthenia gravis total score, improved score of another comparable standardized rating scale that reliably measures MG disease severity) **[medical record documentation required]**; **OR**
6. For patients with a diagnosis of **neuromyelitis optica spectrum disorder (NMOSD)**:
    a. The request is for an eculizumab product (i.e., Soliris, Bkemv, or Epysqli) or ravulizumab (Ultomiris); **AND**
    b. The patient has had a positive clinical response while using the requested agent, as demonstrated by disease stabilization or improvement (e.g., reduced number of relapses, improvement or stabilization of vision or paralysis) **[medical record documentation required]**; **AND**

7. If the request is for Soliris (eculizumab) or a non-preferred eculizumab biosimilar product (e.g., eculizumab-aeeb [Bkemv], etc.), ONE of the following:
    a. The patient has tried and had an inadequate response to the following preferred eculizumab biosimilar product: eculizumab-aagh (Epysqli) **[medical record documentation required]**; **OR**
    b. The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to eculizumab-aagh (Epysqli) that is NOT expected to occur with the requested product **[medical record documentation required]**; **OR**
    c. The patient has a documented serious adverse event that required medical intervention to eculizumab-aagh (Epysqli) that is NOT anticipated with the requested product **[medical record documentation required]**; **AND**
        i. The prescriber has completed and submitted an FDA MedWatch Adverse Event Reporting Form **[medical record documentation required]**; **AND**
8. The patient will NOT be using the requested agent in combination with another agent used to treat the requested indication (**see Combination Agents table below) **[medical record documentation required]**; **AND**
9. The prescriber is a specialist in the area of the patient's diagnosis (e.g., hematologist, neurologist) or has consulted with a specialist in the area of the patient's diagnosis **[medical record documentation required]**; **AND**
10. The requested quantity does NOT exceed the maximum units allowed for the duration of approval (see table below); **AND**
11. For requests for injection or infusion administration of the requested medication in an **inpatient or outpatient hospital setting,** Site of Care Criteria applies (outlined below)*

Duration of Approval: 365 days (1 year)

Combination Agents**

Indication	Medication
Atypical hemolytic uremic syndrome (aHUS)	Eculizumab products (e.g., Soliris, Bkemv, Epysqli), Ultomiris
Generalized myasthenia gravis (gMG)	Eculizumab products (e.g., Soliris, Bkemv, Epysqli), Imaavy, Rystiggo, Ultomiris, Vyvgart, Vyvgart Hytrulo, Zilbrysq
Neuromyelitis optica spectrum disorder (NMOSD)	Eculizumab products (e.g., Soliris, Bkemv, Epysqli), Enspryng, Rituximab products (e.g., Rituxan, Riabni, Ruxience, Truxima), Uplizna, Ultomiris
Paroxysmal nocturnal hemoglobinuria (PNH)	Eculizumab products (e.g., Soliris, Bkemv, Epysqli), Empaveli, Fabhalta, PiaSky, Ultomiris

FDA Label Reference				
Medication	**Indication**	**Dosing^**	**HCPCS**	**Maximum Units***
crovalimab-akkz (PiaSky®) intravenous (IV) infusion, subcutaneous (SC) injection	PNH in patients ≥ 13 years old and weighing at least 40 kg	Loading dose: One IV loading dose given on day 1, followed by 4 additional weekly SC loading doses • ≥ 40 kg to < 100 kg: 1,000 mg IV on day 1, then 340 mg SC on days 2, 8, 15, and 22 • ≥ 100 kg: 1,500 mg IV on day 1, then 340 mg SC on days 2, 8, 15, and 22 Maintenance dose: Given SC starting on day 29 and every 4 weeks thereafter • ≥ 40 kg to < 100 kg: 680 mg SC • ≥ 100 kg: 1,020 mg SC Note: For patients switching from another complement inhibitor (e.g., eculizumab or ravulizumab), the first loading dose should be given no sooner than the time of the next scheduled complement inhibitor administration.	J1307	Initial: 898 Continuation: 1,326

FDA Label Reference				
Medication	**Indication**	**Dosing^**	**HCPCS**	**Maximum Units***
eculizumab (Soliris®) intravenous (IV) infusion	PNH in patients ≥18 years old aHUS in patients ≥2 months old gMG in patients ≥6 years old NMOSD in patients ≥18 years old	PNH: • 600 mg IV weekly for the first 4 weeks, then • 900 mg IV for the 5th dose 1 week later, then • 900 mg IV every 2 weeks thereafter aHUS: ≥ 18 years old: • 900 mg IV weekly for the first 4 weeks, then • 1,200 mg IV for the 5th dose 1 week later, then • 1,200 mg IV every 2 weeks thereafter < 18 years old (weight-based): • ≥ 40 kg: 900 mg IV weekly x 4 doses, then 1,200 mg at week 5, then 1,200 mg every 2 weeks	J1299	**PNH:** Initial: 6,600 Continuation: 11,700 **aHUS:** Initial: 9,000 Continuation: 15,600 **gMG:** Initial: 9,000 Continuation: 15,600

FDA Label Reference				
Medication	**Indication**	**Dosing^**	**HCPCS**	**Maximum Units***
eculizumab-aeeb (Bkemv®) intravenous (IV) infusion		• 30 kg to < 40 kg: 600 mg IV weekly x 2 doses, then 900 mg at week 3, then 900 mg every 2 weeks • 20 kg to < 30 kg: 600 mg IV weekly x 2 doses, then 600 mg at week 3, then 600 mg every 2 weeks • 10 kg to < 20 kg: 600 mg IV weekly x 1 dose, then 300 mg at week 2, then 300 mg every 2 weeks • 5 kg to < 10 kg: 300 mg IV weekly x 1 dose, then 300 mg at week 2, then 300 mg every 3 weeks <u>gMG:</u> ≥ 18 years old: • 900 mg IV weekly for the first 4 weeks, then • 1,200 mg IV for the 5th dose 1 week later, then • 1,200 mg IV every 2 weeks thereafter 6 to < 18 years old (weight-based): • ≥ 40 kg: 900 mg IV weekly x 4 doses, then 1,200 mg at week 5, then 1,200 mg every 2 weeks	Q5152	**NMOSD:** Initial: 9,000 Continuation: 15,600

FDA Label Reference				
Medication	**Indication**	**Dosing^**	**HCPCS**	**Maximum Units***
eculizumab-aagh (Epysqli®) intravenous (IV) infusion		• 30 kg to < 40 kg: 600 mg IV weekly x 2 doses, then 900 mg at week 3, then 900 mg every 2 weeks • 20 kg to < 30 kg: 600 mg IV weekly x 2 doses, then 600 mg at week 3, then 600 mg every 2 weeks • 10 kg to < 20 kg: 600 mg IV weekly x 1 dose, then 300 mg at week 2, then 300 mg every 2 weeks • 5 kg to < 10 kg: 300 mg IV weekly x 1 dose, then 300 mg at week 2, then 300 mg every 3 weeks NMOSD: • 900 mg IV weekly for the first 4 weeks, then • 1,200 mg IV for the 5th dose 1 week later, then • 1,200 mg IV every 2 weeks thereafter	Q5151	
ravulizumab-cwvz (Ultomiris®) intravenous (IV) infusion	PNH in patients ≥1 month old weighing ≥5 kg aHUS in patients ≥1 month old weighing ≥5 kg gMG in patients ≥18 years old weighing ≥40 kg NMOSD in patients ≥18 years old weighing ≥40 kg	PNH or aHUS: Loading and maintenance dosing are weight-based and maintenance doses (MD) are to start 2 weeks after loading dose (LD) at the following regimen: 5 to < 10 kg: 600 mg LD followed by MD of 300 mg every 4 weeks 10 to < 20 kg: 600 mg LD followed by MD of 600 mg every 4 weeks 20 to < 30 kg: 900 mg LD followed by MD of 2,100 mg every 8 weeks	J1303	Initial: 1,590 Continuation: 2,310

FDA Label Reference				
Medication	**Indication**	**Dosing^**	**HCPCS**	**Maximum Units***
		30 to < 40 kg: 1,200 mg LD followed by MD of 2,700 mg every 8 weeks 40 to < 60 kg: 2,400 mg LD followed by MD of 3,000 mg every 8 weeks 60 to < 100 kg: 2,700 mg LD followed by MD of 3,300 mg every 8 weeks ≥100 kg: 3,000 mg LD followed by MD of 3,600 mg every 8 weeks For patients currently treated with eculizumab, LD should be administered at time of next scheduled eculizumab dose. <u>gMG or NMOSD:</u> Loading and maintenance dosing are weight-based and maintenance doses (MD) are to start 2 weeks after loading dose (LD) at the following regimen: 40 to < 60 kg: 2,400 mg LD followed by MD of 3,000 mg every 8 weeks 60 to < 100 kg: 2,700 mg LD followed by MD of 3,300 mg every 8 weeks ≥100 kg: 3,000 mg LD followed by MD of 3,600 mg every 8 weeks For patients currently treated with eculizumab, LD should be administered at time of next scheduled eculizumab dose. (Refer to package insert for full dosing details)		

^Supplemental dosing of eculizumab products (Soliris, Bkemv, Epysqli) is required for aHUS, gMG, and NMOSD in the setting of concomitant plasmapheresis, plasma exchange, fresh frozen plasma infusion, or intravenous immunoglobulin treatment

***Maximum units allowed for duration of approval**

***Site of Care Medical Necessity Criteria**

1. For requests for injection or infusion administration in an **inpatient setting**, the injection or infusion may be given if the above medical necessity criteria are met AND the inpatient admission is NOT for the sole purpose of administering the injection or infusion; **OR**
2. For requests for injection or infusion administration in an **outpatient hospital setting**, the injection or infusion may be given if the above medical necessity criteria are met AND ONE of the following must be met:
    a. History of a severe adverse event following the injection or infusion of the requested medication (i.e., anaphylaxis, seizure, thromboembolism, myocardial infarction, renal failure); **OR**
    b. Conditions that cause an increased risk for severe adverse event (i.e., unstable renal function, cardiopulmonary conditions, unstable vascular access); **OR**
    c. History of mild adverse events that have not been successfully managed through mild pre-medication (e.g., diphenhydramine, acetaminophen, steroids, fluids, etc.); **OR**
    d. Inability to physically and cognitively adhere to the treatment schedule and regimen complexity; **OR**
    e. New to therapy, defined as initial injection or infusion OR less than 3 months since initial injection or infusion; **OR**
    f. Re-initiation of therapy, defined as ONE of the following:
        i. First injection or infusion after 6 months of no injections or infusions for drugs with an approved dosing interval less than 6 months duration; **OR**
        ii. First injection or infusion after at least a 1-month gap in therapy outside of the approved dosing interval for drugs requiring every 6 months dosing duration; **OR**
    g. Requirement of a change in the requested restricted product formulation; **AND**
3. If the Site of Care Medical Necessity Criteria in #1 or #2 above are not met, the injection or infusion will be administered in a **home-based infusion** or physician office setting with or without supervision by a certified healthcare professional.

References: all information referenced is from FDA package insert unless otherwise noted below.

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5. Hillmen P, Muus P, Röth A, et al. Long-term safety and efficacy of sustained eculizumab treatment in patients with paroxysmal nocturnal haemoglobinuria. *Br J Haematol*. 2013 Apr 25.
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12. Parker C, Omine M, Richards S, et al. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. *Blood*. 2005;106(12):3699-3709.
13. Pittock SJ, Berthele A, Fujihara K, et al. Eculizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. *N Engl J Med*. 2019;381:614-25.
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16. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. 2015;85(2):177-189.

Policy Implementation/Update Information: Criteria and treatment protocols are reviewed annually by the Blue Cross NC P&T Committee, regardless of change. This policy is reviewed in Q2 annually.

January 2026: Original medical policy criteria issued. Consolidated “Crovalimab-akkz (PiaSky)”, “Eculizumab (Soliris) and Eculizumab Biosimilars”, and “Ravulizumab-cwvz (Ultomiris)” medical policies into the following “Complement C5 Inhibitors” medical policy. For PNH: Applied consistent diagnostic requirements of flow cytometry, LDH level, and PNH signs/symptoms. For eculizumab products for treatment of PNH, added requirement for trial of Fabhalta in addition to Empaveli and Ultomiris. For aHUS: Added differential diagnosis demonstrating complement-mediated HUS, and requirement of ADAMTS13 activity level greater than 5%. For NMOSD: Added requirement of at least one

attack or relapse in the last 12 months prior to treatment and rule out of alternative diagnoses. For eculizumab products, added requirement for trial and failure of preferred eculizumab biosimilar Epysqli (eculizumab-aagh), and adjusted non-preferred eculizumab products to include Soliris (eculizumab) and Bkemv (eculizumab-aeeb); updated trial and failure criteria to also allow for presence of a documented serious adverse event requiring medical intervention from the preferred eculizumab biosimilar product that is not anticipated with the requested non-preferred eculizumab product, with required submission of an FDA MedWatch Adverse Event Reporting Form. Added requirement to be prescribed by or in consultation with a specialist. **Policy notification given 11/1/2025 for effective date 1/1/2026**.
*Further historical criteria changes and updates for Corporate Medical Policies for each individual drug are available upon request from Medical Policy and/or Corporate Pharmacy.