PHARMACY COVERAGE GUIDELINE

EMPAVELI™ (pegcetacoplan) subcutaneous injection
FABHALTA® (iptacopan) oral
VOYDEYA™ (danicopan) oral
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

EMPAVELI (pegcetacoplan)

➢ **Criteria for initial therapy:** Empaveli (pegcetacoplan) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Hematologist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) confirmed by **BOTH** of the following:
    a. Documentation of high-sensitivity flow cytometry showing the absence or deficiency of glycosylphosphatidylinositol (GPI)-anchored proteins (e.g., CD55, CD59) on at least 2 cell lineages (e.g., granulocytes and red blood cells)

    b. Clinical sign or symptoms of PNH (e.g., red blood cell transfusion dependence, dyspnea, severe fatigue, thrombosis, organ dysfunction, uncontrolled pain)

4. Individual has residual anemia despite use of stable dose (for at least 6 months) of a compliment 5 inhibitor for PNH (see Definitions section) and is requesting **ONE** of the following:
    a. Change from Soliris (eculizumab) to Empaveli by initiating Empaveli while continuing Soliris at current dose, then after 4 weeks of dual therapy, discontinue Soliris before using monotherapy with Empaveli
    b. Change from Ultomiris (ravulizumab) to Empaveli by initiating Empaveli monotherapy no more than 4 weeks after the last dose of Ultomiris

5. Empaveli (pegcetacoplan), Fabhalta (iptacopan) will not be used chronically in combination with Soliris (eculizumab) or Ultomiris (ravulizumab-cwvz) except as noted for the 4-week overlap switching from Soliris (eculizumab) to Empaveli

6. Empaveli (pegcetacoplan), Fabhalta (iptacopan) and Voydeya (danicopan) will not be used in combination

7. Individual has been immunized against *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type B at least 2 weeks prior to first dose according to the most current Advisory Committee on Immunization Practices (ACIP), unless the risks of delaying therapy outweighs the risk of developing a serious infection

8. There is a negative pregnancy test in a woman of childbearing potential before starting treatment

9. There are **NO** FDA-label contraindications such as:
    a. Individual is not currently vaccinated against certain encapsulated bacteria (e.g., *Streptococcus pneumoniae*, *Neisseria meningitidis* types A, C, W, Y and B and *Haemophilus influenzae* type B (unless the risks of delaying treatment outweigh the risks of developing a serious bacterial infection with an encapsulated organism)
    b. Individual has unresolved serious infection caused by encapsulated bacteria

10. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

Initial approval duration: 6 months

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- **Criteria for continuation of coverage (renewal request):** Empaveli (pegcetacoplan) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered for continuation of therapy)**:

  1. Individual continues to be seen by physician specializing in the patient's diagnosis or is in consultation with a Hematologist

  2. Individual's condition has responded while on therapy with response defined as individual has achieved and maintained **TWO** of the following:
     a. Increase or stabilization of hemoglobin
     b. Normalization of absolute reticulocyte count (ARC)
     c. Decrease in frequency of red blood cell (RBC) transfusions
     d. Decrease in lactase dehydrogenase (LDH)
     e. Decrease in pain or fatigue

  3. Individual has been adherent with the medication

  4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

  5. Individual has not developed any FDA-label contraindications

  6. Empaveli (pegcetacoplan), Fabhalta (iptacopan) will not be used chronically in combination with Soliris (eculizumab) or Ultomiris (ravulizumab-cwvz) except as noted for the 4-week overlap switching from Soliris (eculizumab) to Empaveli

  7. Empaveli (pegcetacoplan), Fabhalta (iptacopan) and Voydeya (danicopan) will not be used in combination

  Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

  1. **Off-Label Use of Non-Cancer Medications**

  2. **Off-Label Use of Cancer Medications**

FABHALTA (iptacopan)

- **Criteria for initial therapy:** Fabhalta (iptacopan) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

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1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Hematologist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of **ONE** of the following:
    a. Paroxysmal nocturnal hemoglobinuria (PNH) confirmed by **BOTH** of the following:
        i. Documentation of high-sensitivity flow cytometry showing the absence or deficiency of glycosylphosphatidylinositol (GPI)-anchored proteins (e.g., CD55, CD59) on at least 2 cell lineages (e.g., granulocytes and red blood cells)
        ii. Clinical sign or symptoms of PNH (e.g., red blood cell transfusion dependence, dyspnea, severe fatigue, thrombosis, organ dysfunction, uncontrolled pain)

    b. Biopsy proven immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression with **ALL** of the following:
        i. Urine protein to creatinine ratio (UPCR) is at least 1.5 g/g or greater
        ii. Estimated glomerular filtration rate is at least 20 mL/min/1.73m^2
        iii. On a stable dose of maximally tolerated renin-angiotensin system (RAS) inhibitor with or without a stable dose of a sodium-glucose cotransporter 2 (SGLT-2) inhibitor

4. **For Paroxysmal nocturnal hemoglobinemia only**: Individual has residual anemia despite use of stable dose (for at least 6 months) of a compliment 5 inhibitor for PNH (see Definitions section) and is requesting **ONE** of the following:
    a. Change from Soliris (eculizumab) to Fabhalta by initiating Fabhalta no later than 1 week after the last dose of Soliris
    b. Change from Ultomiris (ravulizumab) to Fabhalta by initiate Fabhalta monotherapy no later than 6 weeks after the last dose of Ultomiris

5. Empaveli (pegcetacoplan), Fabhalta (iptacopan) will not be used chronically in combination with Soliris (eculizumab) or Ultomiris (ravulizumab-cwvz)

6. Empaveli (pegcetacoplan), Fabhalta (iptacopan) and Voydeya (danicopan) will not be used in combination

7. Individual has been immunized against *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type B at least 2 weeks prior to first dose according to the most current Advisory Committee on Immunization Practices (ACIP), unless the risks of delaying therapy outweighs the risk of developing a serious infection

8. There is **NONE** of the following:
    a. Use with a strong CYP2C8 inhibitor (e.g., gemfibrozil)
    b. Use in an individual with severe renal impairment (estimated glomerular filtration rate < 30 mL/min/1.73 m2) with or without hemodialysis
    c. Use in an individual with severe hepatic impairment (Child-Pugh Class C)

9. There are **NO** FDA-label contraindications such as unresolved serious infection caused by encapsulated bacteria

10. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Fabhalta (iptacopan) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by physician specializing in the patient's diagnosis or is in consultation with a Hematologist

2. Individual's condition has responded while on therapy with response defined as **ONE** of the following:
    a. **For Paroxysmal nocturnal hemoglobinemia**: individual has achieved and maintained **TWO** of the following:
        i. Increase or stabilization of hemoglobin
        ii. Normalization of absolute reticulocyte count (ARC)
        iii. Decrease in frequency of red blood cell (RBC) transfusions
        iv. Decrease in lactase dehydrogenase (LDH)
        v. Decrease in pain or fatigue
    b. **For Immunoglobulin A nephropathy** there has been a reduction in the urine protein to creatinine ratio (UPCR)

3. Individual has been adherent with the medication

4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has not developed any FDA-label contraindications

6. Empaveli (pegcetacoplan), Fabhalta (iptacopan) will not be used chronically in combination with Soliris (eculizumab) or Ultomiris (ravulizumab-cwvz)

7. Empaveli (pegcetacoplan), Fabhalta (iptacopan) and Voydeya (danicopan) will not be used in combination

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

  1. **Off-Label Use of Non-Cancer Medications**

  2. **Off-Label Use of Cancer Medications**

VOYDEYA (danicopan)

- **Criteria for initial therapy:** Voydeya (danicopan), and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Hematologist

  2. Individual is 18 years of age or older

  3. Individual has a confirmed diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) confirmed by **BOTH** of the following:
     a. Documentation of high-sensitivity flow cytometry showing the absence or deficiency of glycosylphosphatidylinositol (GPI)-anchored proteins (e.g., CD55, CD59) on at least 2 cell lineages (e.g., granulocytes and red blood cells)

     b. Clinical sign or symptoms of PNH (e.g., red blood cell transfusion dependence, dyspnea, severe fatigue, thrombosis, organ dysfunction, uncontrolled pain)

  4. Individual has residual anemia despite use of stable dose (for at least 6 months) of a compliment 5 inhibitor for PNH (see Definitions section) and is requesting Voydeya (danicopan) as **add-on therapy** to stable dose of Soliris (eculizumab) or Ultomiris (ravulizumab) for at least 6 months for the treatment of extravascular hemolysis (EVH)

  5. Empaveli (pegcetacoplan), Fabhalta (iptacopan) will not be used chronically in combination with Soliris (eculizumab) or Ultomiris (ravulizumab-cwvz)

  6. Empaveli (pegcetacoplan), Fabhalta (iptacopan) and Voydeya (danicopan) will not be used in combination

  7. Individual has been immunized against *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type B at least 2 weeks prior to first dose according to the most current Advisory Committee on Immunization Practices (ACIP), unless the risks of delaying therapy outweighs the risk of developing a serious infection

  8. Liver enzymes have been assessed before treatment initiation and periodically during treatment

  9. Will not be used in an individual with severe hepatic impairment (Child-Pugh Class C)

10. Absolute reticulocyte count is greater than 120×10^9 /L

11. There are **NO** FDA-label contraindications such as unresolved serious infection caused by encapsulated bacteria

12. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Voydeya (danicopan) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by physician specializing in the patient's diagnosis or is in consultation with a Hematologist

2. Individual's condition has responded while on therapy with response defined as individual has achieved and maintained **TWO** of the following:
    a. Increase or stabilization of hemoglobin
    b. Normalization of absolute reticulocyte count (ARC)
    c. Decrease in frequency of red blood cell (RBC) transfusions
    d. Decrease in lactase dehydrogenase (LDH)
    e. Decrease in pain or fatigue

3. Individual has been adherent with the medication

4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has not developed any FDA-label contraindications

6. Empaveli (pegcetacoplan), Fabhalta (iptacopan) will not be used chronically in combination with Soliris (eculizumab) or Ultomiris (ravulizumab-cwvz)

7. Empaveli (pegcetacoplan), Fabhalta (iptacopan) and Voydeya (danicopan) will not be used in combination

Renewal duration: 12 months

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- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

  1. **Off-Label Use of Non-Cancer Medications**

  2. **Off-Label Use of Cancer Medications**

Description:

Empaveli (pegcetacoplan) and Fabhalta (iptacopan) are indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH). Fabhalta is also indicated for reduction of proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) =1.5 g/g. This indication is approved under accelerated approval based on reduction of proteinuria. It has not been established whether Fabhalta slows kidney function decline in patients with IgAN. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.

Voydeya (danicopan) is a complement factor D inhibitor indicated as add-on therapy to Ultomiris (ravulizumab) or Soliris (eculizumab) for the treatment of extravascular hemolysis (EVH) in adults with paroxysmal nocturnal hemoglobinuria (PNH). Voydeya (danicopan) has not been shown to be effective as monotherapy and should only be prescribed as an add-on to Ultomiris (ravulizumab) or Soliris (eculizumab).

PNH is a rare, acquired disorder in which hematopoietic stem cells that causes reduced or absent glycosylphosphatidylinositol (GPI)-anchored proteins on the cell surface. GPI-linked complement inhibitors prevent over activation of the alternative pathway of complement (APC) which is a component of innate immunity. The functional components of APC are C3 and C5 convertases and cytolytic membrane attack complex (MAC). Loss of the GPI-linked complement inhibitors on red blood cells (RBCs) leads to paroxysmal intravascular hemolysis (IVH) and an increased risk for thrombosis, organ dysfunction, and hypocellular or dysplastic bone marrow. Some individuals with PNH may have clinically significant aplastic anemia or myelodysplastic syndrome. Common clinical symptoms include fatigue, dyspnea, hemoglobinuria, abdominal pain, bone marrow suppression, erectile dysfunction, thrombosis, and renal insufficiency.

PNH is categorized into one of three categories: hemolytic (classical) PNH, subclinical PNH and PNH with bone marrow failure. Complement inhibitors including Soliris (eculizumab), Ultomiris (ravulizumab-cwvz), and Empaveli (pegcetacoplan) are primarily used to treat symptomatic hemolytic PNH to manage anemia-related symptoms, thrombosis, pain, and organ dysfunction. Clinical benefit includes stabilization of hemoglobin, decreases in transfusion and reduction in hemolysis. Soliris (eculizumab) and Ultomiris (ravulizumab-cwvz) are both complement 5 inhibitors that target IVH. Soliris administered as an intravenous infusion. Ultomiris is administered as an intravenous infusion in adult or pediatric patients one month of age and older or as a subcutaneous injection for maintenance in adult patients. Subcutaneous dosing of Ultomiris is not approved for use in pediatric patients.

Empaveli (pegcetacoplan) is a pegylated pentadecapeptide that targets complement C3. In binding to complement protein C3 and its activation fragment C3b, pegcetacoplan regulates the cleavage of C3 and the

generation of downstream effectors of complement activation. It acts in the complement cascade that controls both C3b-mediated extravascular hemolysis (EVH) and terminal complement-mediated intravascular hemolysis.

Fabhalta (iptacopan) binds to Factor B of the alternative complement pathway and regulates the cleavage of C3, generation of downstream effectors, and the amplification of the terminal pathway. In PNH, IVH is mediated by the downstream MAC, while EVH is facilitated by C3b opsonization. Iptacopan acts proximally in the alternative pathway of the complement cascade to control both C3b-mediated EVH and terminal complement-mediated IVH. Fabhalta is available as a capsule and is given twice daily.

Empaveli (pegcetacoplan) is administered subcutaneously via an infusion pump at doses 1,080 milligrams twice weekly. For lactase dehydrogenase (LDH) levels greater than 2 times the upper limit of normal (ULN), adjust the dose to every 3 days. The LDH is monitored twice weekly for at least 4 weeks after a dose increase. An Empaveli REMS program requires prescribers to enroll in and educate patients regarding the risks of bacterial infections and the need for preventative vaccinations against encapsulated bacteria.

Voydeya (danicopan) binds reversibly to complement Factor D and selectively inhibits the alternative complement pathway. Voydeya (danicopan) prevents the cleavage of complement Factor B into the Ba and Bb fragments which are required for the formation of the alternative pathway (AP) complement component C3 convertase (C3bBb), the generation of downstream effectors including C3 fragment opsonization, and the amplification of the terminal pathway. In PNH, intravascular hemolysis (IVH) is mediated by the terminal membrane attack complex (MAC), while extravascular hemolysis (EVH) is facilitated by C3 fragment opsonization. Voydeya (danicopan) acts proximally in the alternative pathway of the complement cascade to control preferentially C3 fragment-mediated EVH, while co-administered Ultomiris (ravulizumab) or Soliris (eculizumab) is anticipated to maintain control over MAC-mediated IVH.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Paroxysmal Nocturnal Hemoglobinuria therapies:

Compliment Factor B inhibitor (CFBi)	FABHALTA (iptacopan)
Compliment Factor D inhibitor (CFDi)	VOYDEYA (danicopan)
Compliment 3 inhibitor (C3i)	EMPAVELI (pegcetacoplan)
Compliment 5 inhibitor (C5i)	SOLIRIS (eculizumab)
Compliment 5 inhibitor (C5i)	ULTOMIRIS (ravulizumab)
Compliment 5 inhibitor (C5i)	PIASKY (crovalimab-akkz)

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Resources:

Empaveli (pegcetacoplan) subcutaneous injection product information, revised by Apellis Pharmaceutical, Inc. 02-2024. Available at DailyMed https://dailymed.nlm.nih.gov/dailymed/. Accessed December 02, 2024.

Fabhalta (iptacopan) cap product information, revised by Novartis Pharmaceutical Corporation. 08-2024. Available at DailyMed https://dailymed.nlm.nih.gov/dailymed/. Accessed December 02, 2024.

Voydeya (danicopan) tab product information, revised by Alexion Pharmaceuticals Inc. 04-2024. Available at DailyMed https://dailymed.nlm.nih.gov/dailymed/. Accessed December 02, 2024.

Brodsky RA DeZern AE. Clinical manifestations and diagnosis of paroxysmal nocturnal hemoglobinuria. In: UpToDate, Larson RA, Rosmarin AG (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through November 2024. Topic last updated November 27, 2024. Accessed December 30, 2024.

Brodsky RA. Paroxysmal nocturnal hemoglobinuria: Treatment and prognosis. In: UpToDate, Larson RA, Rosmarin AG (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through November 2024. Topic last updated November 06, 2024. Accessed December 30, 2024.

Cheung CK, Barratt J. IgA nephropathy: Clinical features and diagnosis In: UpToDate, Glassock RJ, Fervenza FC, Coppo R, Lam AQ (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through November 2024. Topic last updated January 05, 2024. Accessed December 30, 2024.

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Makam AN, Suh K, Fahim SM, et al: Iptacopan and Danicopan for Paroxysmal Nocturnal Hemoglobinuria: Effectiveness and Value; Evidence Report. Institute for Clinical and Economic Review, March 13, 2024. https://icer.org/assessment/paroxysmal-nocturnalhemoglobinuria-2024/. Accessed August 06, 2024.

Hillmen P, Szer J, Weitz I, et al. Pegcetacoplan versus Eculizumab in Paroxysmal Nocturnal Hemoglobinuria. NEJM 2021;384(11):1028-1037. Accessed January 18, 2023.