PRIOR AUTHORIZATION POLICY

POLICY: Complement Inhibitors – Empaveli Prior Authorization Policy
- Empaveli™ (pegcetacoplan subcutaneous injection – Apellis)

REVIEW DATE: 05/21/2025; selected revision 08/06/2025

INSTRUCTIONS FOR USE

THE FOLLOWING COVERAGE POLICY APPLIES TO HEALTH BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. CERTAIN CIGNA COMPANIES AND/OR LINES OF BUSINESS ONLY PROVIDE UTILIZATION REVIEW SERVICES TO CLIENTS AND DO NOT MAKE COVERAGE DETERMINATIONS. REFERENCES TO STANDARD BENEFIT PLAN LANGUAGE AND COVERAGE DETERMINATIONS DO NOT APPLY TO THOSE CLIENTS. COVERAGE POLICIES ARE INTENDED TO PROVIDE GUIDANCE IN INTERPRETING CERTAIN STANDARD BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. PLEASE NOTE, THE TERMS OF A CUSTOMER'S PARTICULAR BENEFIT PLAN DOCUMENT [GROUP SERVICE AGREEMENT, EVIDENCE OF COVERAGE, CERTIFICATE OF COVERAGE, SUMMARY PLAN DESCRIPTION (SPD) OR SIMILAR PLAN DOCUMENT] MAY DIFFER SIGNIFICANTLY FROM THE STANDARD BENEFIT PLANS UPON WHICH THESE COVERAGE POLICIES ARE BASED. FOR EXAMPLE, A CUSTOMER'S BENEFIT PLAN DOCUMENT MAY CONTAIN A SPECIFIC EXCLUSION RELATED TO A TOPIC ADDRESSED IN A COVERAGE POLICY. IN THE EVENT OF A CONFLICT, A CUSTOMER'S BENEFIT PLAN DOCUMENT ALWAYS SUPERSEDES THE INFORMATION IN THE COVERAGE POLICIES. IN THE ABSENCE OF A CONTROLLING FEDERAL OR STATE COVERAGE MANDATE, BENEFITS ARE ULTIMATELY DETERMINED BY THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT. COVERAGE DETERMINATIONS IN EACH SPECIFIC INSTANCE REQUIRE CONSIDERATION OF 1) THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT IN EFFECT ON THE DATE OF SERVICE; 2) ANY APPLICABLE LAWS/REGULATIONS; 3) ANY RELEVANT COLLATERAL SOURCE MATERIALS INCLUDING COVERAGE POLICIES AND; 4) THE SPECIFIC FACTS OF THE PARTICULAR SITUATION. EACH COVERAGE REQUEST SHOULD BE REVIEWED ON ITS OWN MERITS. MEDICAL DIRECTORS ARE EXPECTED TO EXERCISE CLINICAL JUDGMENT WHERE APPROPRIATE AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. WHERE COVERAGE FOR CARE OR SERVICES DOES NOT DEPEND ON SPECIFIC CIRCUMSTANCES, REIMBURSEMENT WILL ONLY BE PROVIDED IF A REQUESTED SERVICE(S) IS SUBMITTED IN ACCORDANCE WITH THE RELEVANT CRITERIA OUTLINED IN THE APPLICABLE COVERAGE POLICY, INCLUDING COVERED DIAGNOSIS AND/OR PROCEDURE CODE(S). REIMBURSEMENT IS NOT ALLOWED FOR SERVICES WHEN BILLED FOR CONDITIONS OR DIAGNOSES THAT ARE NOT COVERED UNDER THIS COVERAGE POLICY (SEE "CODING INFORMATION" BELOW). WHEN BILLING, PROVIDERS MUST USE THE MOST APPROPRIATE CODES AS OF THE EFFECTIVE DATE OF THE SUBMISSION. CLAIMS SUBMITTED FOR SERVICES THAT ARE NOT ACCOMPANIED BY COVERED CODE(S) UNDER THE APPLICABLE COVERAGE POLICY WILL BE DENIED AS NOT COVERED. COVERAGE POLICIES RELATE EXCLUSIVELY TO THE ADMINISTRATION OF HEALTH BENEFIT PLANS. COVERAGE POLICIES ARE NOT RECOMMENDATIONS FOR TREATMENT AND SHOULD NEVER BE USED AS TREATMENT GUIDELINES. IN CERTAIN MARKETS, DELEGATED VENDOR GUIDELINES MAY BE USED TO SUPPORT MEDICAL NECESSITY AND OTHER COVERAGE DETERMINATIONS.

CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Empaveli, a complement C3 inhibitor, is indicated for the following uses:[1]
- **Complement 3 glomerulopathy** (C3G), to reduce proteinuria in adults and pediatric patients ≥ 12 years of age.
- **Immune-complex membranoproliferative glomerulonephritis** (IC-MPGN) [primary], to reduce proteinuria in adults and pediatric patients ≥ 12 years of age.
- **Paroxysmal nocturnal hemoglobinuria** (PNH), treatment in adults.

Empaveli is given subcutaneously, via an infusion pump or an on-body injector.[1] Empaveli is intended for use under the guidance of a healthcare professional; after proper training, Empaveli may be self-administered or be administered by a caregiver.

Empaveli has a Boxed Warning regarding serious infections caused by encapsulated bacteria.[1] Empaveli is only available through a restricted access program, Empaveli Risk Evaluation and Mitigation Strategy (REMS).

Disease Overview

C3G and IC-MPG

C3G and IC-MPGN (also known as immunoglobulin-mediated membranoproliferative glomerulonephritis [MPGN]) are in a group of kidney disorders termed MPGN.[2-5] C3G and IC-MPGN are rare and chronic complement-mediated kidney diseases.[2-4] MPGN occurs due to glomerular deposition of immune complexes and/or complement factors.[2] IC-MPGN is classified as "idiopathic" or "primary" when an underlying cause is not identified and "secondary" when the condition is due to an underlying disease (e.g., infection or autoimmune condition).[2,5] The incidence of idiopathic IC-MPGN is unknown; the estimated global annual incidence of C3G is between 1 and 3 cases per one million people.[2] Patients with either condition are at risk of kidney failure; risk of progression to kidney failure is up to 30% to 35% of patients with C3G and idiopathic IC-MPGN within 10 years of diagnosis. There are overlapping pathologic features of C3G and IC-MPGN; dysregulation of the complement pathway plays a key role in the pathogenesis of both diseases. In C3G, overactivation of the alternative complement pathway leads to accumulation of C3 in the glomerulus, resulting in kidney inflammation and damage. The role of the complement system in the pathogenesis of IC-MPGN is less well-understood; both the classical and alternative complement pathway are activated but the mechanisms by which immune complexes are deposited are unknown. Patients with C3G and IC-MPGN may exhibit similar clinical signs and symptoms at disease onset, including proteinuria, hematuria, decreased kidney function, nephrotic syndrome, and hypertension. Although biopsy is needed for a definitive diagnosis, distinguishing between the two diseases remain a challenge due to overlap in the composition of the glomerular deposits. In addition, it is unclear whether idiopathic IC-MPGN and C3G are distinct entities or two aspects of the same disease as the two conditions share similar clinical presentations and patient outcomes, including similar risk of progression to kidney disease and prevalence of nephrotic syndrome. Current treatment options, which primarily target inflammation and slow down the progression of kidney disease, include corticosteroids, immunosuppressive drugs, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and complement inhibitors.[2-5] It is unclear if immunosuppressive treatment (e.g., calcineurin inhibitors, cyclophosphamide, corticosteroids, mycophenolate mofetil) in patients with primary IC-MPGN is beneficial; outcomes data are scant and controversial.[6] In addition, long term benefit of corticosteroids and immunosuppressive therapies are uncertain.[2]

PNH

PNH is a rare, genetic disorder of hematopoietic stem cells.[7,8] The mutation in the X-linked gene phosphatidylinositol glycan class A (PIGA) results in a deficiency in the glycosylphosphatidylinositol (GPI) protein, which is responsible for anchoring other protein moieties to the surface of the erythrocytes. Loss of anchoring of these proteins causes cells to hemolyze and leads to complications such as hemolytic anemia, thrombosis, and peripheral blood cytopenias. PNH is a clinical diagnosis

that should be confirmed with peripheral blood flow cytometry to detect the absence or severe deficiency of GPI-anchored proteins on at least two lineages.[7,9] Prior to the availability of complement inhibitors, only supportive measures in terms of managing the cytopenias and controlling thrombotic risk were available. Supportive measures include platelet transfusion, immunosuppressive therapy for patients with bone marrow failure, use of erythropoietin for anemias, and aggressive anticoagulation.

Dosing Recommendations When Switching to Empaveli from eculizumab intravenous infusion (Soliris®, biosimilars) or Ultomiris (ravulizumab-cwvz) for Treatment of PNH

For patients switching from eculizumab intravenous [IV] infusion (Soliris, biosimilars) to Empaveli, initiate Empaveli while continuing eculizumab at the current dose.[1] After 4 weeks, discontinue eculizumab and continue Empaveli monotherapy. For patients switching from Ultomiris® (ravulizumab-cwvz IV infusion), initiate Empaveli no more than 4 weeks after the last dose of Ultomiris.

Clinical Efficacy in C3G and IC-MPGN

The efficacy of Empaveli in reducing proteinuria in patients with native kidney C3G, native kidney IC-MPGN, or recurrent C3G following kidney transplant was shown in the VALIANT study. Enrolled patients were ≥ 12 years of age and weigh ≥ 30 kg with biopsy-proven, native kidney or post-transplant recurrent C3G or native kidney primary IC-MPGN. In addition, patients had estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2, proteinuria ≥ 1 g/day, and urine protein-to-creatinine ratio (UPCR) ≥ 1 g/g. Patients were required to be on stable and optimized doses of ACE inhibitors, ARBs, and/or sodium-glucose cotransporter-2 (SGLT2) inhibitors for at least 12 weeks before randomization and throughout the 26-week placebo-controlled period. Immunosuppressants (e.g., steroids < 20 mg/day, mycophenolate mofetil, tacrolimus) had to be stable for at least 12 weeks before randomization and throughout the placebo-controlled period. In total, 124 patients were included in the study; 88 patients (71%) had native kidney C3G, 27 patients (22%) had native kidney primary IC-MPN, and 8 patients (6%) had post-kidney transplant recurrent C3G.

The primary efficacy endpoint was the log-transformed ratio of UPCR (sampled from first morning urine collections) at Week 26 compared to baseline. At Week 26, the geometric mean UPCR ratio relative to baseline was 0.33 in the Empaveli group and 1.03 in the placebo group; resulting in a 68% reduction in UPCR from baseline in the Empaveli group compared to placebo ($P < 0.0001$). The treatment effect was consistent across all subgroups, including disease type, age, transplant status (C3G patients), sex, race, baseline disease characteristics (eGFR, UPCR), and immunosuppressant use. A key secondary endpoint was the proportion of patients who achieved the composite renal endpoint, defined as a ≥ 50% reduction in UPCR and stable eGFR (≤ 15% reduction from baseline) during the 26-week placebo-controlled period. This endpoint was achieved by 49% of patients in the Empaveli group vs. 3% of patients in the placebo group (odds ratio of 27, $P < 0.0001$). In total, 60% of patients in the Empaveli group achieved a ≥ 50% reduction in UPCR from baseline to Week 26 compared to 5% of patients in the placebo group; and

68% vs. 59% of patients in the Empaveli vs. placebo, respectively, who had a stable eGFR at Week 26. Over the first 6 months of treatment, Empaveli reduced the loss of kidney function compared with placebo. The efficacy of Empaveli in pediatric patients ≥ 12 years of age was similar to that for adults.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Empaveli. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Empaveli as well as the monitoring required for adverse events and long-term efficacy, approval requires Empaveli to be prescribed by or in consultation with a physician who specializes in the condition being treated.

- **Empaveli™ (pegcetacoplan subcutaneous injection – Apellis) is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):**

FDA-Approved Indications

1. **Complement 3 Glomerulopathy.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial therapy. Approve for 6 months if the patients ALL of the following (i, ii, iii, iv, v, and vi)
     - **i.** Patient is ≥ 12 years of age; AND
     - **ii.** The diagnosis has been confirmed by biopsy; AND
     - **iii.** Patient has a urine protein-to-creatinine ratio ≥ 1.0 g/g; AND
     - **iv.** Patient has an estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2; AND
     - **v.** Patient has been on stable doses of at least ONE of the following for ≥ 12 weeks prior to starting Empaveli (a, b, or c):
       - **a)** Angiotensin converting enzyme inhibitor; OR
       - **b)** Angiotensin receptor blocker; OR
       - **c)** Sodium-glucose transporter-2 inhibitor; AND
     - **vi.** The medication is prescribed by or in consultation with a nephrologist; OR
   - **B)** Patient is Currently Receiving Empaveli. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, iv, and v):
     - **i.** Patient is ≥ 12 years of age; AND
     - **ii.** The diagnosis has been confirmed by biopsy; AND
     - **iii.** According to the prescriber, patient has had a response to Empaveli; AND
       Note: Examples of a response are a reduction in urine-to-creatinine ratio from baseline, reduction in proteinuria from baseline.
     - **iv.** Patient has an estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2; AND
     - **v.** The medication is prescribed by or in consultation with a nephrologist.

2. **Immune-Complex Membranoproliferative Glomerulonephritis, Primary.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial therapy. Approve for 6 months if the patients ALL of the following (i, ii, iii, iv, v, and vi)
     - **i.** Patient is ≥ 12 years of age; AND
     - **ii.** The diagnosis has been confirmed by biopsy; AND
     - **iii.** Patient has a urine protein-to-creatinine ratio ≥ 1.0 g/g; AND
     - **iv.** Patient has an estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2; AND
     - **v.** Patient has been on stable doses of at least ONE of the following for ≥ 12 weeks prior to starting Empaveli (a, b, or c):
       a) Angiotensin converting enzyme inhibitor; OR
       b) Angiotensin receptor blocker; OR
       c) Sodium-glucose transporter-2 inhibitor; AND
     - **vi.** The medication is prescribed by or in consultation with a nephrologist; OR
   - **B)** Patient is Currently Receiving Empaveli. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, iv, and v):
     - **i.** Patient is ≥ 12 years of age; AND
     - **ii.** The diagnosis has been confirmed by biopsy; AND
     - **iii.** According to the prescriber, patient has had a response to Empaveli; AND
       Note: Examples of a response are a reduction in urine-to-creatinine ratio from baseline, reduction in proteinuria from baseline.
     - **iv.** Patient has an estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2; AND
     - **v.** The medication is prescribed by or in consultation with a nephrologist.

3. **Paroxysmal Nocturnal Hemoglobinuria.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Paroxysmal nocturnal hemoglobinuria diagnosis was confirmed by peripheral blood flow cytometry results showing the absence or deficiency of glycosylphosphatidylinositol-anchored proteins on at least two cell lineages; AND
     - **iii.** For a patient transitioning to Empaveli from eculizumab intravenous infusion (Soliris, biosimilar), the prescriber attests that eculizumab will be discontinued 4 weeks after starting Empaveli; AND
     - **iv.** The medication is prescribed by or in consultation with a hematologist; OR
   - **B)** Patient is Currently Receiving Empaveli. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** According to the prescriber, patient is continuing to derive benefit from Empaveli; AND
       Note: Examples of benefit include increase in or stabilization of hemoglobin levels, decreased transfusion requirements or transfusion

independence, reductions in hemolysis, improvement in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score.

iii. The medication is prescribed by or in consultation with a hematologist.

CONDITIONS NOT COVERED

- **Empaveli™ (pegcetacoplan subcutaneous injection – Apellis) is(are) considered not medically necessary for ANY other use(s) including the following (this list may not be all inclusive; criteria will be updated as new published data are available):**

1. **Concomitant Use with Eculizumab Intravenous Infusion (Soliris, biosimilars) for > 4 weeks.** There is no evidence to support concomitant use of Empaveli with eculizumab. However, to reduce the risk of hemolysis from abrupt treatment discontinuation in a patient switching from eculizumab to Empaveli, the patient should be initiated on Empaveli while continuing eculizumab. After 4 weeks, discontinue eculizumab and continue Empaveli monotherapy.

2. **Concomitant Use with Fabhalta (iptacopan capsule), PiaSky (crovalimab-akkz intravenous infusion or subcutaneous injection), Ultomiris (ravulizumab-cwvz intravenous infusion), or Voydeya (danicopan tablets).** There is no evidence to support concomitant use of Empaveli with Fabhalta, PiaSky, Ultomiris, or Voydeya.

REFERENCES

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7. Cançado RD, da Silva Araújo A, Sandes AF, et al. Consensus statement for diagnosis and treatment of paroxysmal nocturnal haemoglobinuria. *Hematol Transfus Cell Ther*. 2021;43:341-348.
8. Shah N, Bhatt H. Paroxysmal Nocturnal Hemoglobinuria. [Updated 2023 Jul 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK562292/. Accessed on May 13, 2025.
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	05/24/2023
Selected Revision	**Paroxysmal Nocturnal Hemoglobinuria:** Criterion regarding patient transitioning to Empaveli from Soliris or Ultomiris was revised to remove Ultomiris. **Conditions Not Covered** **:** Criterion regarding concomitant use with Soliris or Ultomiris for > 4 weeks was revised to remove Ultomiris. Criterion regarding concomitant use of Empaveli with Fabhalta or Ultomiris was added.	01/17/2024
Selected Revision	**Paroxysmal Nocturnal Hemoglobinuria:** Initial approval duration was changed from 4 months to 6 months.	02/28/2024
Annual Revision	**Paroxysmal Nocturnal Hemoglobinuria:** For patients who are currently receiving Empaveli, the Note regarding examples of benefit of Empaveli is updated to include "improvement in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score." Conditions Not Covered : Voydeya is added to the criterion addressing concomitant use of Empaveli with Fabhalta (iptacopan capsule) or Ultomiris (ravulizmab-cwvz intravenous infusion or subcutaneous injection).	05/29/2024
Annual Revision	**Paroxysmal Nocturnal Hemoglobinuria:** Biosimilars to Soliris were added to criteria where only Soliris was previously noted. **Conditions Not Covered** **:** Biosimilars to Soliris were added to criteria where only Soliris was previously noted. Ultomiris subcutaneous injection was removed from criteria since the manufacturer has decided not to market the product. PiaSky was added to the list of medications that should not be used concomitantly with Empaveli.	05/21/2025
Selected Revision	**Complement 3 Glomerulopathy:** This FDA approved indication was added to the policy. **Immune-Complex Membranoproliferative Glomerulonephritis.** This FDA approved indication was added to the policy.	08/06/2025