Paroxysmal Nocturnal Hemoglobinuria Agents
EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO235

Description
Pegcetacoplan (Empaveli) is a subcutaneous complement inhibitor of C3. Iptacopan (Fabhalta) is an oral complement factor B inhibitor. Danicopan (Voydeya) is an oral complement factor D inhibitor.

Length of Authorization
- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
danicopan (Voydeya)	Extravascular hemolysis (EVH) in paroxysmal nocturnal hemoglobinuria (PNH)	50 mg/100 mg tablets dose pack	180 tablets/30 days
		100 mg tablets	180 tablets/30 days
pegcetacoplan (Empaveli)	Paroxysmal nocturnal hemoglobinuria (PNH)	1,080 mg/20 mL vial	160 mL (8 vials)/28 days
iptacopan (Fabhalta)	Paroxysmal nocturnal hemoglobinuria (PNH)	200 mg capsules	60 capsules/30 days
	Reduction of proteinuria in primary IgA nephropathy (IgAN) at risk of rapid disease progression	200 mg capsules	60 capsules/30 days

Initial Evaluation

I. **Pegcetacoplan (Empaveli), iptacopan (Fabhalta),** and **daniopan (Voydeya)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a hematologist or immunologist; **AND**
   C. Provider attestation of a diagnosis of **paroxysmal nocturnal hemoglobinuria** (**PNH**) confirmed via flow cytometry with PNH clones of at least 10%; **AND**
   D. The request is for **pegcetacoplan (Empaveli)** or **iptacopan (Fabhalta)**; **AND**
      1. Member has at least one of the following indications for treatment:
         i. Transfusion dependence (hemoglobin is 7 g/dL or less)
         ii. Hemoglobin is 9 g/dL or less with symptoms of anemia (e.g. disabling fatigue)
         iii. The member has experienced a thromboembolic event
         iv. Presence of organ damage secondary to chronic hemolysis (e.g., renal insufficiency, pulmonary insufficiency/hypertension)
         v. High LDH activity (≥ 1.5 x ULN) with clinical symptoms

vi. Patient has symptoms associated with smooth muscle dystonia (e.g., abdominal pain, dysphagia, esophageal spasm, erectile dysfunction); **AND**

2. The request is for pegcetacoplan (Empaveli); **OR**
3. The request is for iptacopan (Fabhalta); **AND**
    i. Documentation that treatment with pegcetacoplan (Empaveli) has been ineffective, contraindicated, or not tolerated; **AND**
4. Provider attestation that medication will not be used in combination with other complement inhibitor therapy (e.g., eculizumab [Soliris], ravulizumab [Ultomiris], danicopan [Voydeya]); **OR**

E. The request is for **danicopan (Voydeya)**; **AND**
1. Member has been established on therapy with a complement component factor 5 (C5) inhibitor (e.g., eculizumab [Soliris], ravulizumab [Ultomiris]) at therapeutic maintenance doses; **AND**
2. Documentation of persistent anemia consistent with **extravascular hemolysis (EVH) in paroxysmal nocturnal hemoglobinuria (PNH) [PNH-EVH]** defined by all the following:
    i. Hemoglobin ≤ 9.5 g/dL
    ii. Absolute reticulocyte count ≥ 120 x 10^9/L; **AND**
3. Medication will be used in combination with a complement component 5 (C5) inhibitor (e.g., eculizumab [Soliris], ravulizumab [Ultomiris])

II. **Iptacopan (Fabhalta)** may be considered medically necessary when the following criteria are met:

A. Member is 18 years of age or older; **AND**
B. Medication is prescribed by, or in consultation with, a nephrologist or immunologist; **AND**
C. A diagnosis of **Primary immunoglobulin A nephropathy (IgAN)** when the following are met:
1. Diagnosis of Primary immunoglobulin A nephropathy (IgAN) has been confirmed by a kidney biopsy; **AND**
2. Documentation of elevated protein levels in urine as indicated by proteinuria ≥ 1 g/day or urine protein to creatinine ratio (UPCR) ≥ 1.5 g/g; **AND**
3. Member is not currently receiving dialysis and has not undergone kidney transplant; **AND**
4. Treatment with a renin-angiotensin system (RAS) inhibitor for ≥ 3 months [e.g., angiotensin converting enzyme (ACE) inhibitor (e.g., enalapril, lisinopril); angiotensin receptor blocker (ARB) (e.g., valsartan, irbesartan)] has been ineffective, not tolerated, or all are contraindicated; **AND**
D. Treatment will not be used in combination with atrasentan (Vanrafia), budesonide (Tarpeyo), or sparsentan (Filspari)

III. Pegcetacoplan (Empaveli), iptacopan (Fabhalta), and danicopan (Voydeya) are considered investigational when used for all other conditions, including but not limited to:
   A. Paroxysmal nocturnal hemoglobinuria in pediatric patients
   B. Paroxysmal nocturnal hemoglobinuria in combination with other complement inhibitors [with the exception of danicopan (Voydeya) in combination with C5 inhibitors]
   C. Amyotrophic lateral sclerosis (ALS)
   D. Macular degeneration
   E. Hemolytic uremic syndrome
   F. Myasthenia gravis
   G. Neuromyelitis optica spectrum disorder (NMOSD)
   H. Thrombotic microangiopathy
   I. Immune thrombocytopenia
   J. Immunoglobulin A (IgA) vasculitis (Henoch-Schoenlein purpura) in pediatric patients
   K. Geographic atrophy (GA) secondary to age-related macular degeneration
   L. Secondary IgA nephropathy

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. The member has a diagnosis of **Primary immunoglobulin A nephropathy (IgAN); AND**
   A. The request is for iptacopan (Fabhalta); **AND**
      i. Member is not currently receiving dialysis and has not undergone kidney transplant; **AND**
      ii. Treatment will not be used in combination with atrasentan (Vanrafia), budesonide (Tarpeyo), or sparsentan (Filspari); **AND**
      iii. Member has exhibited improvement or stability of disease symptoms (e.g., reduction in proteinuria <1 g/day or urine protein to creatinine ratio (UPCR) < 1.5 g/g); **OR**
IV. The member has a diagnosis of **Paroxysmal nocturnal hemoglobinuria (PNH)**; **AND**
   A. Member has exhibited improvement or stability of disease symptoms (e.g., increased hemoglobin, reduction in LDH, reduction in reticulocyte count, reduction in transfusion frequency); **AND**
   B. For **pegcetacoplan (Empaveli)** or **iptacopan (Fabhalta):**

i. Provider attestation that medication will not be used in combination with other complement inhibitor therapy (e.g., eculizumab [Soliris], ravulizumab [Ultomiris], danicopan [Voydeya]); **OR**

C. For **danicopan (Voydeya):**

i. The medication will be used in combination with a C5 inhibitor (e.g., eculizumab [Soliris], ravulizumab [Ultomiris])

Supporting Evidence

Paroxysmal nocturnal hemoglobinuria (PNH)

I. Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disease characterized by complement-mediated hemolysis, leading to debilitating fatigue, anemia, dyspnea, bone pain, bleeding/bruising, thrombosis, and bone marrow dysfunction. Curative therapy for PNH is allogenic hematopoietic stem cell (HSC) transplant; however, given safety and cost limitations, transplant is reserved for those with severe and refractory disease manifestations.

II. Diagnosis and treatment of this condition is highly specialized. To ensure an appropriate diagnosis and that the benefits of treatment outweigh the risks, prescribing by, or in consultation with, a specialist is required. Confirmation of diagnosis by Flow Cytometry is currently the most accepted method to confirm diagnosis of PHN. Therefore, this is required given the rarity of PNH and to ensure medication is medically necessary as the proportion of PNH III cells, which are cells completely missing GPI-anchored proteins on the cell surface, can be diluted by a recent transfusion or depleted due to a recent hemolytic crisis.

III. Pegcetacoplan (Empaveli) and iptacopan (Fabhalta) have not been evaluated in combination with other complement inhibitors. There is currently one open-label, single-arm, Phase 2 trial that is evaluating the use of iptacopan (Fabhalta) and eculizumab (Soliris) combination use; however, study results are not mature. Therefore, the efficacy and safety of combination use remains unknown at this time.

IV. Treatment for PNH is indicated when signs and symptoms are present with a diagnosis confirmed via flow cytometry. Signs and symptoms include transfusion dependence (defined as a Hgb ≤7 g/dL), symptoms of anemia with a Hgb ≤9 g/dL, thrombosis, organ dysfunction, and debilitating fatigue associated with hematologic lab values that are out of the normal range (e.g., low Hgb, increased LDH, etc.). Smooth muscle dystonia can occur due to hemolysis induced depletion of nitric oxide, and is associated with abdominal pain, dysphagia, erectile dysfunction, and esophageal spasm. Nitric oxide depletion or pulmonary emboli can also be associated with pulmonary hypertension in some patients. The chronic hemolysis and associated anemia experienced by PNH patients can lead to disabling fatigue along with acute and chronic kidney disease. Anemia, and therefore the need for transfusions, can be multifactorial with hemolysis, iron deficiency, and bone marrow failure, all of which contribute to low Hgb levels. The increased risk of thrombosis in PNH has a variety of potential contributing factors to the hypercoagulability state including prothrombotic microparticles, high levels of free Hgb, complement activation, and the absence/deficiency of GPI-linked proteins.

V. The C5 inhibitors, eculizumab (Soliris) and ravulizumab (Ultomiris) (± supportive care), have become standard of care given their ability to improve disease manifestations. However, these only target intravascular hemolysis, leaving opportunity for extravascular hemolysis in the liver and spleen. Despite treatment, anemia and the need for continued blood transfusions may persist in some patients. For the majority of patients C5 inhibitors are successful treatment options as they have been shown to improve Hg, LDH levels, reticulocyte count, and/or reduce transfusion frequency. The safety profile of these therapies is well established.

VI. **Pegcetacoplan (Empaveli)**

- Pegcetacoplan (Empaveli) is a C3 complement inhibitor and acts proximally to the complement cascade preventing intravascular and extravascular hemolysis. It is the first complement inhibitor that may be self-administered via a subcutaneous infusion pump; although, therapy may also be administered by a healthcare provider.
- To date, pegcetacoplan (Empaveli) has been evaluated in adult patients. Clinical trials are underway to evaluate the safety and efficacy of pediatric patients. However, other therapies [e.g., ravulizumab (Ultomiris)] have been evaluated and are FDA-approved down to one month of age. Until sufficiently evaluated in pediatric patients, pegcetacoplan (Empaveli) should be reserved for the FDA-approved age group(s) given the availability of alternate avenues of care (e.g., other FDA-approved medications, enrolment in clinical trials).
- The pivotal trial for pegcetacoplan (Empaveli) was an open label, randomized, Phase 3 study in comparison to eculizumab (Soliris) (PEGASUS trial). Patients were 18 years of age or older, had a hemoglobin of less than 10.5 mg/dL (mean 8.7 g/dL) while on stable doses of eculizumab (Soliris) for at least three months before enrollment, 75% received a blood transfusion in the last year (over 50% of patients received four or more).
- Eighty patients were enrolled in the trial. Seventy-five percent had received a blood transfusion in the last year (over 50% of patients received four or more). Primary outcome: change in Hg from baseline at week 16. Secondary outcomes: proportion of transfusion-free patients, change in reticulocyte count, lactate dehydrogenase (LDH) level, and Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F). The normalization of hematologic variables was also evaluated. Endpoints were tested in a hierarchical manner, the primary outcome was tested for superiority, and the secondary outcomes were tested for non-inferiority (NI). The primary outcome met superiority, and transfusion rate and reticulocyte count met NI. Normalization of hematologic variables (Hg, reticulocytes, LDH) were favorable for pegcetacoplan (Empaveli). Pegcetacoplan (Empaveli) was also evaluated in Phase 1 and 2 open-label, single-arm trials in complement inhibitor-naïve patients. Improvements were seen in Hg, LDH, reticulocytes, and FACIT-F scores in a small number of patients.
- The safety and efficacy of pegcetacoplan (Empaveli) has been established for 1,080 mg (20 mL) twice weekly. In the clinical trials, three patients discontinued therapy given lack of efficacy, following this, a protocol amendment was made to allow an increase in the dose to every three days, and two patients received the increased dose. Data regarding the safety and efficacy of 1,080 mg (20mL) three times a week has been proven in

scientific literature, and the pegcetacoplan (Empaveli) prescribing information recommends adjusting the dosing to 1,080mg (20 mL) every three days for lactate dehydrogenase (LDH) levels greater than 2× the upper limit of normal (ULN).

- With the exception of the four-week overlap to get patients established on pegcetacoplan (Empaveli), therapy has not been evaluated in combination with other complement inhibitors. It is advised that complement inhibitors are not abruptly discontinued. If switching from eculizumab (Soliris), therapy should be overlapped for four weeks with pegcetacoplan (Empaveli). For those switching from ravulizumab (Ultomiris), pegcetacoplan (Empaveli) should be started no more than four weeks after the last dose of ravulizumab (Ultomiris). Maintenance therapy with more than one complement inhibitor therapy is not expected to have additional efficacy and is expected to have serious safety implications (e.g., serious infections caused by encapsulated bacteria). Thus, maintenance on more than one complement inhibitor therapy is not indicated at this time.
- The bulk of evidence is from patients that were refractory to the C5 inhibitor eculizumab (Soliris), and it is expected that pegcetacoplan (Empaveli) will be utilized heavily in this treatment setting; however, given the alternative protein target of this therapy, coupled with evidence data support from Phase 1 and 2 trials, it is expected pegcetacoplan (Empaveli) will be efficacious as a first-line treatment. A clinical trial is underway to evaluate this further.

VII. **Iptacopan (Fabhalta)**

- The safety and efficacy of iptacopan (Fabhalta) was evaluated in two Phase 3, multicenter, open-label trials. Both trials were studied in adult patients aged 18 years and older. Safety and efficacy have not been evaluated for pediatric patients.
- The APPPLY-PNH trial was a 24-week multicenter, open-label, randomized, Phase 3 trial which compared iptacopan (Fabhalta) against standard of care (SOC) eculizumab (Soliris) or ravulizumab (Ultomiris) in adult patients with PNH, as evidenced by a diagnosis via high-sensitivity flow cytometry with a clone size ≥10% and a hemoglobin less than 10 g/dL. Patients were required to be on a stable dose of eculizumab (Soliris) or ravulizumab (Ultomiris) for at least 6 months prior to randomization and 56% of patients had received a blood transfusion in the 6 months prior to enrollment. The primary endpoint was the percentage of participants achieving a hematological response, defined as an increase from baseline in Hb ≥2 g/dL in the absence of RBC transfusions, and demonstrated statistically significant change compared to SOC (difference: 80.3% [95% CI: 71.3-87.6]; p<0.0001). The other primary endpoint, percentage of participants achieving sustained Hb ≥12 g/dL in the absence of RBC transfusions, also demonstrated statistical significance compared to SOC (difference: 67.0% [95% CI: 56.3-76.9]; p<0.0001).
- The APPOINT-PNH trial was an open-label, single arm, Phase 3 trial that enrolled 40 treatment naïve, adult patients with a high-sensitivity flow cytometry clone size of ≥10%, Hgb <10 g/dL, and a LDH >1.5 ULN. The primary endpoint, percentage achieving hematological response, defined as an increase from baseline in Hb ≥2 g/dL in the

absence of red blood cell (RBC) transfusions, was met (92.2% (95% CI: 82.5-100)). One key secondary endpoint was percentage achieving hematological response defined as having Hb ≥12 g/dL in the absence of RBC transfusions, which was also met (62.8% (95% CI: 47.5-77.5)).

- The safety and efficacy of iptacopan (Fabhalta) has been established for the 200mg capsules twice daily. In the APPLY trial 82.3% of patients experienced a treatment emergent adverse event (TEAE) as compared to 80% of the comparator group. The most common TEAEs in the iptacopan (Fabhalta) group were headache (16.1%), diarrhea (14.5%), and nasopharyngitis (11.3%). Serious TEAEs occurred in 9.7% of the iptacopan (Fabhalta) patients while 14.3% of patients in the comparator group experienced a serious TEAE. No patient in the iptacopan (Fabhalta) group experienced a hemolysis related serious TEAE while one patient in the comparator group experienced breakthrough hemolysis and another experienced extravascular hemolysis. No patients discontinued due to adverse events or deaths. In the APPOINT trial, no breakthrough hemolysis events, or major adverse vascular events (MAVEs) were reported during the 24-week core treatment period. Treatment emergent adverse events (TEAEs)were reported in 93% of patients with 65% considered mild in severity. The most common TEAEs were headache (27.5%), COVID-19 (15%), and upper respiratory tract infection (12.5%). Serious TEAEs were reported in 10% of patients with one case of bacterial pneumonia, COVID-19, type II diabetes mellitus, and cataract. No patients discontinued due to side effects and no deaths were reported.

VIII. Both iptacopan (Fabhalta) and pegcetacoplan (Empaveli) have studies (APPLY-PNH and PEGASUS, respectively) demonstrating their efficacy in patients who were not clinically stable on anti-C5 therapy. There are no direct comparison trials available demonstrating superiority of iptacopan (Fabhalta) to pegcetacoplan (Empaveli), the use of the most cost-effective treatment option should be considered. For these reasons, trial of pegcetacoplan (Empaveli) is required prior to use of iptacopan (Fabhalta), unless contraindicated, not tolerated, or ineffective.

IX. **Danicopan (Voydeya)**

- Danicopan (Voydeya) is a complement factor D inhibitor FDA-approved to treat extravascular hemolysis (EVH) symptoms in patients with an incomplete response to C5 inhibitors [eculizumab (Soliris) or ravulizumab (Ultomiris)] at maintenance doses. Paroxysmal nocturnal hemoglobinuria with extravascular hemolysis (PNH-EVH) occurs in roughly 10-20% of patients with PNH and is the result of uncontrolled accumulation of C3 which targets RBC in the spleen and liver. Clinically evident EVH presents as symptomatic anemia, increased reticulocytes and LDH ≥1.5 x ULN in the absence of other causes of anemia (e.g., folate deficiency, bleeding). Paroxysmal nocturnal hemoglobinuria with extravascular hemolysis (PNH-EVH) may limit the hematologic benefits of C5 inhibitors, resulting in symptomatic anemia, transfusion dependency, and fatigue. It does not affect mortality or risk of thrombosis, but it does negatively affect quality of life.
- Danicopan (Voydeya) was studied in a 12-week, Phase 3, randomized, double-blind, placebo-controlled clinical trial (ALPHA) in 73 adult patients with PNH, who were stable

on C5 inhibitor therapy for at least six months prior to enrollment and experiencing EVH, defined as hemoglobin(Hgb) ≤9.5 g/dL with absolute reticulocyte count ≥120 x10^9/L. Patients received danicopan (Voydeya) (n=49) or placebo (n=24) orally three times a day in addition to C5 background therapy [eculizumab (Soliris) or ravulizumab (Ultomiris)]. Sixty-three patients were included in the primary statical analysis; all 73 were included in the safety outcomes.

- The primary endpoint was the change in hemoglobin (Hgb) from baseline to the end of week 12 in the primary efficacy set [the first 63 patients on danicopan (Voydeya)]. The primary endpoint met statistical significance with a mean change in Hgb from baseline of 2.94 g/dL in the danicopan (Voydeya) arm and 0.50 g/dL in the placebo arm; a difference of 2.44 g/dL (1.69-3.20; p<0.001). Secondary endpoints including percentage of participants achieving ≥2 g/dL Hgb increase, transfusion avoidance, mean change in the FACIT-fatigue scores, and absolute reticulocyte counts were also met, achieving statistically significant results compared to placebo. A 12-week extension of ALPHA and an additional ongoing two-year open label period, where all patients on placebo changed to receiving danicopan (Voydeya) in addition to C5 therapy, demonstrated sustained benefit in the endpoints through the reported 48-weeks of data.
- Danicopan (Voydeya) was well tolerated with the most commonly reported TEAE as headaches (11%). Other commonly reported AEs occurring over 5% of the 73 danicopan (Voydeya) treated patients included vomiting, pyrexia, and increase in serum triglycerides. No deaths occurred in the study. Danicopan (Voydeya) also includes the same REMS program as the other complement factors due to risk of infections caused by encapsulated bacteria.
- The quality of evidence is moderate considering this was a well-designed randomized, placebo, controlled, Phase 3 clinical trial that demonstrated statistically significant and clinically meaningful changes in the primary and secondary endpoints. These endpoints portray symptom relief, better functioning, and greater health-related quality of life assessments in PNH patients who are experiencing EVH and are not adequately controlled on a C5 inhibitor therapy.
- The dosing of danicopan (Voydeya) is 150 mg three times a day and can be increased to 200 mg three times a day if the patients' Hgb has not increased by 2 g/dL in four weeks. During the clinical trial, 44 patients (60.3%) required increasing to 200 mg to achieve the 2 g/dL increase.

Primary Immunoglobulin A Nephropathy (IgAN)

I. Primary Immunoglobulin A Nephropathy (IgAN), also called Berger's disease, is a rare kidney disorder characterized by deposits of immune complexes containing galactose-deficient IgA in the glomerular mesangium leading to glomerulosclerosis, and renal failure. Although previously considered a benign condition, IgAN is now recognized to cause end-stage renal disease (ESRD) in 30% of affected individuals.

II. The Kidney Disease Improving Global Outcomes (KDIGO) guideline indicates IgAN can only be diagnosed with a kidney biopsy. While there are several prognostic scoring tools that have been developed to assist in predicting kidney outcomes of IgAN patients (i.e., MEST-C, International IgAN Prediction Tool, etc.) there are currently no validated diagnostic serum or urine biomarkers.

III. Due to the complexities related to diagnosis monitoring and management of IgAN patients, therapy for this disease space should be initiated by or in consultation with a specialist such as nephrologist or immunologist.

IV. There are no curative therapies for IgAN. Supportive care with blood pressure management, use of renin-angiotensin system (RAS) blockers (ACEis or ARBs), and lifestyle modifications are the recommended initial interventions for IgAN treatment. Patients with proteinuria level of ≥1 g/day (or urine protein to creatinine ratio (UPCR) > 1.5 g/g) despite 3 to 6 months of initial treatment, are at high risk of progression to kidney failure. The Kidney Disease Improving Global Outcomes guideline for the management of glomerular diseases strongly recommends proteinuria reduction < 1 g/day as a treatment goal for high-risk IgAN.

V. As of July 2025, there are four therapies approved for the treatment of IgAN via the FDA's accelerated approval pathway: budesonide (Tarpeyo), sparsentan (Filspari), iptacopan (Fabhalta), and atrasentan (Vanrafia). Tarpeyo and Filspari have received full FDA-approval based on positive clinical response based on reduced proteinuria and long-term kidney data. Continued approval of Fabhalta and Vanrafia will be contingent on confirmation of a clinical benefit is expected later 2025 and early 2026.

VI. The accelerated approval for iptacopan (Fabhalta) for the treatment of the IgAN indication was based on the Phase 3 randomized, double-blind APPLAUSE-IgAN trial (NCT04578834). The study enrolled adults with biopsy-proven IgAN (eGFR ≥20 mL/min/1.73m^2, and UPCR ≥1g/g on a stable dose of maximally-tolerated RAS inhibitor therapy with or without a stable dose of a sodium-glucose contransporter-2 [SGLT2] inhibitor). The trial excluded participants on chronic dialysis or kidney transplantation for end-stage kidney disease as these are considered clinical outcomes of interest. The interim efficacy analysis was based on the first 250 patients with eGFR ≥30 mL/min/1.73 m^2 who had completed or discontinued the study prior to the month 9 visit. The two primary endpoints of the study for the interim and final analysis, respectively, are proteinuria reduction at 9 months as measured by 24-hour UPCR, and the annualized total eGFR slope over 24 months. Patients receiving iptacopan (Fabhalta) had a proteinuria reduction of 44% compared with 9% in the placebo group at 9 months, translating to a clinically significant 38% reduction for iptacopan (Fabhalta) versus placebo. Moreover, the benefit remained consistent across all subgroups, including those with SGLT2 inhibitor use.

VII. The most common adverse reactions in adults with IgAN were upper respiratory tract infection (9%), lipid disorder (6%), and abdominal pain (6%). Iptacopan (Fabhalta) label carries the same risks and precautions as it does for PNG. The label for iptacopan (Fabhalta) includes a Boxed Warning regarding an increased risk for serious and life-threatening infections caused by

encapsulated bacteria, including *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type B. Due to this risk, iptacopan (Fabhalta) is only available through a Risk Evaluation and Mitigation Strategies (REMS) program. Vaccination against encapsulated bacteria or antibacterial drug prophylaxis (in patients who are not up to date with vaccines) is recommended. Iptacopan (Fabhalta) is contraindicated in individuals with unresolved serious infections.

VIII. The quality of evidence for iptacopan (Fabhalta) is considered low. The APPLAUSE-IgAN clinical program consists of an ongoing trial, alluding to a short-term indication of efficacy. Reduction in proteinuria < 1 g/day is an objective surrogate marker for IgAN. However, it falls shy of predicting long-term patient outcomes such as progression to ESRD, dialysis dependence and overall mortality in ESRD. The Kidney Health Initiating workgroup and National Kidney Foundation recommend the use of dual (primary and confirmatory) endpoints of proteinuria reduction as well as slope of eGFR decline. At this time, effect of iptacopan (Fabhalta) on eGFR is unknown compared to other agents on the market. Currently, all four approved therapies for IgAN demonstrate comparable reductions in UPCR; but ultimately, confirmatory eGFR data from both iptacopan (Fabhalta) and atrasentan (Vanrafia) will be essential for evaluating their impact on long term kidney function.

IX. As of July 2025, no clinical trials support the combined use of multiple novel therapies in IgAN. While it is known that multiple pathophysiologic mechanisms contribute to kidney function loss in patients with IgAN, particularly those at risk of progressive decline, targeting these mechanisms concurrently may be necessary. In clinical practice, this could mean combining standard of care therapies with one or more agents. In the absence of updated clinical guidelines and supporting evidence to allow combination use of IgAN therapies (e.g., atrasentan (Vanrafia), budesonide (Tarpeyo), sparsentan (Filspari), iptacopan (Fabhalta), etc.), concurrent use is contraindicated and considered experimental and investigational.

Investigational or Not Medically Necessary Uses

I. Pegcetacoplan (Empaveli), iptacopan (Fabhalta), and danicopan (Voydeya) have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Paroxysmal nocturnal hemoglobinuria in pediatric patients
   B. Paroxysmal nocturnal hemoglobinuria in combination with other complement inhibitors [with the exception of danicopan (Voydeya) in combination with C5 inhibitors]
   C. Amyotrophic lateral sclerosis (ALS)
   D. Macular degeneration
   E. Hemolytic uremic syndrome
   F. Myasthenia gravis
   G. Neuromyelitis optica spectrum disorder
   H. Thrombotic microangiopathy

I. Immune thrombocytopenia
J. Immunoglobulin A (IgA) vasculitis (Henoch-Schoenlein purpura) in pediatric patients
K. Geographic atrophy (GA) secondary to age-related macular degeneration
L. Secondary IgA nephropathy

Appendix

I. Complement inhibitor administration for PNH:

Therapy	Dose/Frequency	Duration of medication coverage (maintenance)	Route
iptacopan (Fabhalta)	200 mg twice daily	1 day	PO
pegcetacoplan (Empaveli)	1,080 mg (20 mL) twice weekly	3-4 days	SQ
eculizumab (Soliris)	Loading dose: 600 mg weekly for four weeks, 900 mg on the fifth week Maintenance, therapeutic dosing: 900 mg every two weeks thereafter	2 weeks	IV
ravulizumab (Ultomiris)	One loading dose (based on weight) 2,400 mg-3,000 mg, then maintenance treatment/therapeutic dosing (based on weight) starting two weeks later: 3,000 mg – 3,600 mg every eight weeks	8 weeks	IV
danicopan (Voydeya)	Start 150 mg three times a day orally, with or without food. Depending on clinical response, can increase to 200 mg three times a day.	1 day	PO

II. Switch therapy guidance for PNH:

- Transitioning from eculizumab (Soliris) to pegcetacoplan (Empaveli): Overlap therapy for four weeks (i.e., initiate pegcetacoplan [Empaveli] while continuing eculizumab [Soliris] at the current dose). Then, discontinue eculizumab (Soliris) after four weeks of treatment with pegcetacoplan (Empaveli) - to utilize pegcetacoplan (Empaveli) as monotherapy.
- Transitioning from ravulizumab (Ultomiris) to pegcetacoplan (Empaveli): Once the last dose of ravulizumab (Ultomiris) is administered, pegcetacoplan (Empaveli) should be initiated within four weeks of the infusion. No further doses of ravulizumab (Ultomiris) should be administered while pegcetacoplan (Empaveli) treatment is active.
- Transitioning from eculizumab (Soliris) to iptacopan (Fabhalta): initiate iptacopan (Fabhalta) no later than one week after the last dose of eculizumab (Soliris).
- Transitioning from ravulizumab (Ultomiris) to iptacopan (Fabhalta): initiate iptacopan (Fabahalta) no later than 6 weeks after the last dose of ravulizumab (Ultomiris).
- Transitioning from eculizumab (Soliris) to ravulizumab (Ultomiris) or vice versa: reference prescribing information for guidance.

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
budesonide (Tarpeyo)	Primary IgA nephropathy; at high risk of progression
sparsentan (Filspari) and atrasentan (Vanrafia)	Primary IgA nephropathy; at high risk of progression

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated policy name from "Paroxysmal Nocturnal Hemoglobinuria Agents" to "Proximal Complement Inhibitors." Added pathway to coverage for iptacopan (Fabhalta) for the treatment of primary IgAN. Updated supporting evidence, E/I, references. Added related policies.	07/2025
Added danicopan (Voydeya) tablets to the policy. Updated supporting evidence.	08/2024
Added iptacopan (Fabhalta) capsules to the policy. Updated supporting evidence and other investigational conditions.	02/2024
Policy created	08/2021