Drug Coverage Policy

Effective Date.....08/01/2025
Coverage Policy Number.....IP0614
Policy Title.....Fabhalta

Complement Inhibitors – Fabhalta

- Fabhalta® (iptacopan capsules – Novartis)

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.

Overview
Fabhalta, a Factor B inhibitor, is indicated for the following uses:[1]

- **Complement 3 glomerulopathy** (C3G), to reduce proteinuria in adults.
- **Paroxysmal nocturnal hemoglobinuria** (PNH), in adults.

- **Primary immunoglobulin A nephropathy** (IgAN), for the reduction of proteinuria in adults at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g.

For the IgAN indication, Fabhalta was approved under accelerated approval based on reduction of proteinuria.[1] 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.

Fabhalta has a Boxed Warning about serious meningococcal infections.[1] Fabhalta is only available through a restricted access program, Fabhalta Risk Evaluation and Mitigation Strategy (REMS).

Disease Overview

C3G

C3G, an ultra-rare complement-mediated kidney disease, is chronic and slowly progressive.[2,3] The prevalence of C3G is challenging to estimate accurately; registry data suggest that incidence and prevalence are approximately 1 to 3 cases per million and 5 cases per million, respectively in the US.[2] C3G results from deregulation and consequently overactivation of the alternative pathway of the complement system, which allows the complement cascade to progress and activate all effector levels.[2,3] In addition, deregulated complement results in deposition of C3b on target surfaces of the glomerulus. Urine analysis is typically the first step in diagnosis and typically shows proteinuria and hematuria. Renal biopsy is essential for diagnosis; histopathologic features of C3G are characterized by C3 deposits, absence or minimal immunoglobulin deposits within the glomeruli, evidence of glomerular inflammation, and mesangial cell proliferation. There are no approved disease-specific therapy for C3G. Standard of care includes supportive care, which includes blood pressure control with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers to reduce proteinuria and slow down kidney damage. Immunosuppressants such as corticosteroids, mycophenolate mofetil, cyclophosphamide, and rituximab are typically used to treat moderate to severe disease. Immunosuppressives may be used to reduce the production of autoantibodies and to reduce the inflammatory response. Some patients may be treated with plasma exchange or plasmapheresis, which are used to replace the defective complement proteins and to remove autoantibodies and other forms of debris.

PNH

PNH is a rare, genetic disorder of hematopoietic stem cells.[4,5] 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.[4,6] Prior to the availability of complement inhibitors, only supportive care to manage the cytopenias and control 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.

IgAN

IgAN is the most common primary glomerular disease in the world and it is the leading cause of chronic kidney disease (CKD) and kidney failure.[7] The disease is slowly progressive; approximately 25% to 30% of patients develop kidney failure within 20 to 25 years of presentation. The management of IgAN is focused on supportive care to slow the rate of disease progression. IgAN is characterized by a single histopathologic criterion of predominant or co-dominant IgA deposits on kidney biopsy; however, it is well recognized that the disease exhibits heterogeneity in clinical and pathological features. Hypertension and proteinuria are major risk factors for the progression of

CKD. Guidelines from Kidney Diseases: Improving Global Outcomes (KDIGO) note that proteinuria reduction to < 0.5 g/day, a surrogate marker of improved kidney outcomes in IgAN, is a reasonable target.

Clinical Efficacy

C3G

The efficacy of Fabhalta for the treatment of C3G was studied in a randomized, double-blind, placebo-controlled study.[1] All patients were ≥ 18 years of age with biopsy-confirmed native kidney C3G with a urine protein-to-creatinine ratio (UPCR) ≥ 1.0 g/g and estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2. Patients were randomized to receive either Fabhalta 200 mg twice daily (BID) or placebo for 6 months, followed by a 6-month open-label treatment period in which all patients received Fabhalta. All patients were on a maximally recommended or tolerated dose of an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) for ≥ 90 days.[8] In addition, patients could be receiving other therapies (e.g., corticosteroid and/or mycophenolate mofetil) at baseline if they were on stable doses for 90 days prior to randomization and throughout the study.[1] The primary efficacy endpoint was the log-transformed ratio to baseline in UPCR (sampled from a 24-hour urine collection) at 6 months.

At Month 6, the geometric mean UPCR ratio relative to baseline was 0.70 (95% confidence interval [CI]: 0.57, 0.85) for the Fabhlata group and 1.08 (95% CI: 0.88, 1.31) for the placebo group, resulting in a 35% reduction in the 24-hour UPCR from baseline in the Fabhalta group compared with placebo (P = 0.0028).[1] At 6 months, compared with patients in the placebo group, patients treated with Fabhalta had a 7-fold higher odds (P = 0.0166) of achieving a composite renal endpoint, defined as a ≥ 50% reduction in 24-hour UPCR compared to baseline and stable or improved eGFR compared to baseline (≤ 15% reduction in eGFR). There was no difference between the groups in the proportion of patients with stable or improved eGFR compared to baseline at 6 months; 90% in the Fabhalta group vs. 89% in the placebo group; however, a greater proportion of patients in the Fabhalta group achieved a ≥ 50% reduction in 24-hour UPCR compared to baseline (30% vs. 6%, respectively).

IgAN

The efficacy of Fabhalta was evaluated in one Phase 3, pivotal, 24-month trial in patients ≥ 18 years of age with IgAN.[1,9] Eligible patients had biopsy-proven IgAN, eGFR ≥ 30 mL/min/1.73 m^2, and a UPCR ≥ 1.0 g/g on a stable dose of maximally-tolerated renin-angiotensin system inhibitor for 3 months with or without a stable dose of a sodium-glucose cotransporters 2 (SGLT2) inhibitor. Patients were randomized to Fabhalta 200 mg BID or placebo for 24 months while remaining on supportive care. Fabhalta resulted in a statistically and clinically meaningful reduction in proteinuria compared to placebo. Interim efficacy is reported at Month 9.

The primary efficacy endpoint was the change from baseline in the 24-hour UPCR (based on 24-hour urine sample) at Month 9.[1,9] The primary analysis was based on an interim data cutoff of August 15, 2023. At Month 9, the primary endpoint was significantly greater with Fabhalta vs. placebo in the interim analysis set (comprised of the first 250 patients randomized in the study); the geometric least squares mean percent change in UPCR from baseline was -44% vs. -9%, respectively. This resulted in a statistically significant relative reduction from baseline in UPCR for the Fabhalta vs. placebo group (geometric mean ratio 0.617; 95% CI: 0.514, 0.740; P < 0.001), corresponding to a 38% relative reduction with Fabhalta. For Fabhalta, the UPCR changed from 1.9 g/g at baseline to 1.0 g/g at Month 9; for placebo, the change was from 2.0 g/g at baseline to 1.7 g/g at Month 9.

Coverage Policy

Policy Statement
Prior Authorization is required for prescription benefit coverage of Fabhalta. 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 Fabhalta as well as the monitoring required for adverse events and long-term efficacy, approval requires Fabhalta to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required where noted in the criteria. Documentation may include, but not limited to, chart notes, laboratory tests, claims records, and/or other information.

Fabhalta is considered medically necessary when the following is met:

FDA-Approved Indication

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 patient meets ALL of the following (i, ii, iii, iv, v, vi, and vii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has not received a kidney transplant in the past; AND
     - **iii.** The diagnosis has been confirmed by biopsy; AND
     - **iv.** Patient has a urine protein-to-creatinine ratio ≥ 1.0 g/g; AND
     - **v.** Patient has an estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2; AND
     - **vi.** Patient has received the maximum or maximally tolerated dose of ONE of the following for ≥ 90 days prior to starting Fabhalta (a or b):
       - **a)** Angiotensin converting enzyme inhibitor; OR
       - **b)** Angiotensin receptor blocker; AND
     - **vii.** The medication is prescribed by or in consultation with a nephrologist; OR
   - **B)** Patient is Currently Receiving Fabhalta. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, iv, v, and vi):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has not received a kidney transplant in the past; AND
     - **iii.** The diagnosis has been confirmed by biopsy; AND
     - **iv.** According to the prescriber, patient has had a response to Fabhalta; AND
       Note: Examples of a response are a reduction in urine protein-to-creatinine ratio from baseline, reduction in proteinuria from baseline.
     - **v.** Patient has an estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2; AND
     - **vi.** The medication is prescribed by or in consultation with a nephrologist.

2. **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 the following (i, ii, and iii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Diagnosis was confirmed by peripheral blood flow cytometry results showing the absence or deficiency of glycosylphosphatidylinositol-anchored proteins on at least two cell lineages **[documentation required]**; AND
     - **iii.** The medication is prescribed by or in consultation with a hematologist.
   - **B)** Patient is Currently Receiving Fabhalta. Approve for 1 year if the patient meets 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 Fabhalta; 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.

3. **Primary Immunoglobulin A Nephropathy.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 9 months if the patient meets ALL of the following (i, ii, iii, iv, v, and vi):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** The diagnosis has been confirmed by biopsy **[Documentation Required]**; AND
     - **iii.** Patient is at high risk of disease progression, defined by meeting BOTH of the following (a and b):
       - **a)** Patient meets ONE of the following [(1) or (2)]:
         (1) Proteinuria ≥0.5 g/day **[Documentation Required]**; OR
         (2) Urine protein-to-creatinine ratio ≥ 1.5 g/g **[Documentation Required]**; AND
       - **b)** Patient has received the maximum or maximally tolerated dose of ONE of the following for ≥ 12 weeks prior to starting Fabhalta [(1) or (2)]:
         (1) Angiotensin converting enzyme inhibitor; OR
         (2) Angiotensin receptor blocker; AND
     - **iv.** Patient has received ≥ 3 months of optimized supportive care, including blood pressure management, lifestyle modification, and cardiovascular risk modification, according to the prescriber; AND
     - **v.** Patient has an estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2; AND
     - **vi.** The medication is prescribed by or on consultation with a nephrologist.
   - **B)** Patient is Currently Receiving Fabhalta. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, iv, and v):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** The diagnosis has been confirmed by biopsy **[Documentation Required]**; AND
     - **iii.** According to the prescriber, patient has had a response to Fabhalta; AND
       Note: Examples of a response are a reduction in urine protein-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 on consultation with a nephrologist.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Fabhalta for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Concomitant Use with Another Complement Inhibitor**. There is no evidence to support concomitant use of Fabhalta with another complement inhibitor.
   Note: Examples of complement inhibitors are Empaveli (pegcetacoplan subcutaneous injection), PiaSky (crovalimab-akkz intravenous infusion or subcutaneous injection), Soliris

(eculizumab intravenous infusion), Ultomiris (ravulizumab-cwzy intravenous infusion), and Voydeya (danicopan tablets).

References

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3. Ayehu G, Atari M, Hassanein M, Jhaveri KD. C3 glomerulopathy. Available at: https://www.ncbi.nlm.nih.gov/books/NBK609090/#article-169701.s4. Last updated on November 5, 2024. Accessed on March 25, 2025
4. 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.
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6. Roth A, Maciejewski J, Nishinura JI, et al. Screening and diagnostic clinical algorithm for paroxysmal nocturnal hemoglobinuria: Expert consensus. *Eur J Haematol*. 2018;101(1):3-11.
7. Kidney Diseases: Improving Global Outcomes (KDIGO) 2024 clinical practice guidelines for the management of immunoglobulin A nephropathy (IgAN) and immunoglobulin A vasculitis (IgAV). Draft published online ahead of print. Available at: https://kdigo.org/wp-content/uploads/2024/08/KDIGO-2024-IgAN-IgAV-Guideline-Public-Review-Draft.pdf. Accessed on March 25, 2025.
8. Bomback AS, Kavanagh D, Vivarelli M, et al. Alternative complement pathway inhibition with iptacopan for the treatment of C3 glomerulopathy-study design of the APPEAR-C3G trial. *Kidney Int Rep*. 2022;7:2150-2159.
9. Perkovic V, Barratt J, Rovin B, et al. Alternative complement pathway inhibition with iptacopan in IgA nephropathy. *N Engl J Med*. 2025;392(6):531-543.

Revision Details

Type of Revision	Summary of Changes	Date
New	New policy	04/01/2024
Selected Revision	**Paroxysmal Nocturnal Hemoglobinuria:** Initial approval duration was changed from 4 months to 6 months.	06/01/2024
Selected Revision	**Primary Immunoglobulin A Nephropathy:** **Added** this condition and criteria for approval to the policy. **Conditions Not Covered:** Concomitant Use with Another Complement Inhibitor: **Added** Piasky (crovalimab-akkz intravenous infusion or subcutaneous injection) and Voydeya (danicopan tablets) to the Note that lists examples of complement inhibitors.	11/01/2024
Selected Revision	**Paroxysmal Nocturnal Hemoglobinuria,** Patient is currently receiving Fabhalta: "Improvement in	12/15/2024

	Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score" was added to the Note of examples of benefit. **Primary Immunoglobulin A Nephropathy:** The criterion requiring that the patient is at high risk of disease progression, defined by ONE of the following: urine-to-protein-creatinine ratio ≥ 1.5 g/g OR proteinuria ≥ 1 g/day was revised to require that the patient is at high risk of disease progression, defined by urine-to-protein-creatinine ratio ≥ 1.5 g/g OR proteinuria ≥ 0.5 g/day.	
Annual Revision	**Complement 3 Glomerulopathy:** This condition and criteria for approval were added to the policy.	05/15/2025
Selected Revision	**Primary Immunoglobulin A Nephropathy.** **Added** documentation requirements.	07/01/2025
Selected Revision	**Paroxysmal Nocturnal Hemoglobinuria.** Initial Therapy **Added** documentation to the diagnostic statement. Patient is Currently Receiving Fabhalta. **Added** documentation to the beneficial response statement.	08/01/2025

The policy effective date is in force until updated or retired.