Original Effective Date: 06/27/2024
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Last P&T Approval/Version: 10/30/2024
Next Review Due By: 07/2025
Policy Number: C27697-A

Fabhalta (iptacopan)

PRODUCTS AFFECTED

Fabhalta (iptacopan)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Paroxysmal nocturnal hemoglobinuria (PNH), Primary immunoglobulin A nephropathy (IgAN)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by-case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH):
   1. Documentation of diagnosis of Paroxysmal nocturnal hemoglobinuria (PNH)
      AND

2. Prescriber attests that member has been vaccinated against *Streptococcus pneumoniae, Neisseria meningitides (serogroups A, C, W, Y and B),* and *Haemophilus influenzae* type B at least 2 weeks prior to iptacopan treatment, if not previously vaccinated
   AND
3. Documentation of baseline labs and status [DOCUMENTATION REQUIRED]:
   a) Hemoglobin level
      AND
   b) Lactate dehydrogenase level which is 1.5 times the upper limit of the normal range (within the last 30 days). Submit laboratory results with reference range.
      AND
   c) Documentation that member is blood-transfusion dependent, defined by having a transfusion within the last 12 months and ONE of the following: hemoglobin level less than 9 g/dL in the presence of symptoms, or hemoglobin less than 7 g/dL without symptoms (*Lab should be drawn before transfusion or at least one month since last transfusion)
   AND
4. Documentation member meets ONE of the following criteria: Member has history of thrombotic event(s) attributable to PNH (i.e. arterial/venous thrombosis, hepatic vein thrombosis, etc.) or major adverse vascular events from thromboembolism, Member has symptoms of PNH that inhibit the patient's quality of life (i.e. anemia, fatigue, difficulty swallowing, thromboses, frequent paroxysms of pain, recurrent abdominal pain, erectile dysfunction, chronic kidney disease, organ damage secondary to chronic hemolysis), OR Member is pregnant and the potential benefit outweighs potential fetal risk
   AND
5. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Fabhalta (iptacopan) include: serious hypersensitivity to iptacopan or any of the excipients, initiation in patients with unresolved serious infection caused by encapsulated bacteria.]

B. PRIMARY IMMUNOGLOBULIN A NEPHROPATHY (IgAN):
1. Documented diagnosis of Primary Immunoglobulin A Nephropathy (IgAN)
   AND
2. Documentation diagnosis was confirmed by kidney biopsy
   AND
3. Documentation that member has failed to achieve a reduction in proteinuria under 1 gram/day while receiving maximally tolerate doses of a Renin-angiotensin-system (RAS) inhibitor (ACE inhibitor or ARB) for at least 3 months
   AND
4. Documentation that member has had a trial and failure of ONE formulary preferred glucocorticoid for at least 2 months
   AND
5. Documentation that member's urine protein-to-creatinine ratio [UPCR] ≥1.5 (consistent with FDA-approved labeling) and eGFR ≥30 mL/min/1.73 m2
   NOTE: UPCR ≥ 1.5 indicates a risk of rapid progression
   AND
6. Prescriber attests to or clinical reviewer has found member is not currently receiving dialysis or has not undergone kidney transplant
   AND
7. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Fabhalta (iptacopan) include: serious hypersensitivity to iptacopan or any of the excipients, initiation in patients with unresolved serious infection caused by encapsulated bacteria.]

CONTINUATION OF THERAPY:

A. PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH):
1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
   AND
2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
   AND
3. Documentation of disease improvement or stabilization by any of the following: decrease in serum LDH, hemoglobin level above baseline, or reduction in the need for blood transfusions [DOCUMENTATION REQUIRED]

B. PRIMARY IMMUNOGLOBULIN A NEPHROPATHY (IgAN):
1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
   AND
2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
   AND
3. Documentation of positive clinical response as demonstrated by low disease activity and/or improvements in the condition's signs and symptoms

DURATION OF APPROVAL:
Initial authorization: 6 months, Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:
Prescribed by or in consultation with a board-certified hematologist or nephrologist. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:
18 years of age and older

QUANTITY:
200 mg by mouth twice daily

Maximum Quantity Limits – 2 capsules per day

PLACE OF ADMINISTRATION:
The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Complement Factor B Inhibitors

FDA-APPROVED USES:
Indicated for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH), and for the 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.

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired clonal disorder caused by a somatic mutation of the phosphatidylinositol glycan- complementation class A (PIG-A) gene in hematopoietic stem cells. The disorder results in a deficiency of glycosylphosphatidylinositol (GPI), which serves as an anchor for several cell surface proteins including the terminal complement regulator, CD59. The absence of CD59 from the surface of the affected PNH red blood cells (RBCs) renders them susceptible to terminal complement- mediated lysis. The subsequent chronic hemolysis is the primary clinical manifestation of the disease and leads to disabling morbidities that include anemia, fatigue, thrombosis, pain, and impaired quality of life. Lactate dehydrogenase (LDH) is released during RBC destruction and grossly elevated serum LIH is a common finding in patients with PNH. Treatment includes supportive treatments (corticosteroids), treatment changing the course of the disease (eculizumab), and potential curative treatment (allogeneic bone marrow transplantation).

Fabhalta is the first targeted complement factor B inhibitor. It acts proximally in the complement cascade to control both intravascular and extravascular hemolysis, while Soliris and Ultomiris are effective in preventing intravascular hemolysis only. Extravascular hemolysis may contribute to the need for continued blood transfusions despite C5 inhibitor therapy.

Clinical Studies
NCT04558918- APPLY-PNH- Study to Evaluate the Efficacy and Safety of Twice Daily Oral LNP023 in Adult PNH Patients Despite Anti-C5 Antibody Treatment
Study Population- Inclusion: aged ≥18 years; primary diagnosis of PNH confirmed by high-sensitivity flow cytometry with clone size ≥10% ; ongoing treatment with stable dose eculizumab or ravulizumab for ≥6 months; Hb <10 g/dL; vaccination against Neisseria meningitidis, Streptococcus pneumoniae, and Haemophilus influenzae infections Exclusion: ECU dose interval ≤11 days, RAV dose interval < 8 weeks; hereditary complement deficiency; history of hematopoietic stem cell transplantation; laboratory evidence of bone marrow failure (reticulocytes <100x10E9/L; platelets <30x10E9/L; neutrophils <500x10E6/L); active bacterial, viral or fungal infection within 14 days prior to study; history of recurrent invasive infections caused by encapsulated organisms; major concurrent comorbidities including but not limited to severe kidney disease, advanced cardiac disease, severe pulmonary disease or hepatic disease that in the opinion of the investigator precludes participant's participation in the study. *Phase, Study Design, Sample Size*- Randomized, multicenter, open-label, active comparator-controlled study evaluating the safety and efficacy of LNP023 in patients with PNH N=97
Outcomes: LNP023 met the primary efficacy endpoints, demonstrating superior efficacy to eculizumab and ravulizumab and had a favorable safety profile in patients with PNH and anemia despite prior anti-C5 treatment at week 24. 51/62 iptacopan-treated patients and 0/35 C5 inhibitor-treated patients had a sustained hemoglobin increase of ≥2 g/dL independent of blood transfusions from baseline (P<0.0001). 42/62 iptacopan-treated patients and 0/35 C5 inhibitor-treated patients achieved hemoglobin levels of ≥12 independent of blood transfusions from baseline (P<0.0001). 2 patients (3%) in the Iptacopan group

experienced a serious adverse event. 1 iptacopan-treated patient had a major adverse vascular event (transient ischemic attack) unrelated to iptacopan and continued treatment. Most common adverse events (≥10%) at 24 weeks in the Iptacopan and anti-C5 groups were headache (19% vs 3%), nasopharyngitis (16% vs 17%), and diarrhea (15% vs 6%). 2 patients from the iptacopan group had breakthrough hemolysis and 6 patients had clinical breakthrough hemolysis. No patients discontinued iptacopan or C5 inhibitor due to an adverse reaction.

NCT04820530- APPOINT-PNH- Study to Evaluate Efficacy and Safety of Twice Daily Oral Iptacopan (LNP023) in Adult PNH Patients Who are Naïve to Complement Inhibitor Therapy

Study Population- Inclusion: Aged ≥18 years; primary diagnosis of PNH confirmed by high-sensitivity flow cytometry with clone size ≥10%; Hb <10 g/dL; LDH >1.5x ULN; vaccination against Neisseria meningitidis, Streptococcus pneumoniae, and Haemophilus influenzae infections Exclusion: prior treatment with anti-C5 antibody; hereditary complement deficiency; history of hematopoietic stem cell transplantation; laboratory evidence of bone marrow failure (reticulocytes <100x10E9/L; platelets <30x10E9/L; neutrophils <500x10E6/L); active bacterial, viral or fungal infection within 14 days prior to study; history of recurrent invasive infections caused by encapsulated organisms; major concurrent comorbidities including but not limited to severe kidney disease, advanced cardiac disease, severe pulmonary disease or hepatic disease that in the opinion of the investigator precludes participant's participation in the study. Phase, Study Design, Sample Size- Multicenter, open-label, single-arm study evaluating the safety and efficacy of LNP023 in patients with PNH N=40

Outcomes: Iptacopan monotherapy met the primary efficacy endpoint demonstrating efficacy and safety at week 24. 77.5% (31/40) patients that had a sustained hemoglobin increase of ≥2 g/dL independent of blood transfusions from baseline (P<0.0001). 2 patients (5%) experienced a serious adverse event. Most common adverse events (≥10%) at 24 weeks were headache (28%), nasopharyngitis (15%), viral infection (18%) and rash (10%). No patients experienced clinical breakthrough hemolysis or major adverse vascular events. No patients discontinued iptacopan due to an adverse reaction.

Fabhalta is also indicated for rapidly progressing Primary Immunoglobulin A Nephropathy (IgAN). Per the KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases, kidney biopsy is the “gold standard” for diagnostic evaluation of glomerular disease. The guideline further notes that IgAN can only be diagnosed with a kidney biopsy (Chapter 2, reference 3). Additionally, the use of an ACE inhibitor or ARB up to a maximally tolerated or allowed dose is considered first line therapy for the treatment of hypertension and proteinuria. The guideline defines a high risk for progressive disease as proteinuria greater than 0.75 to 1 gram despite the use of optimized supportive care, including an ACE inhibitor or ARB, for at least 90 days. For those patients who remain at high risk of progressive CKD despite the maximized supportive care, immunosuppressive drugs should be considered. Fabhalta received accelerated approval for the indication of IgAN and confirmatory studies are ongoing.

Studied against placebo in a multicenter, randomized, double-blind study (APPLAUSE-IgAN), Fabhalta was found to reduce proteinuria 38% over placebo (44% for Fabhalta vs. 9% for placebo reduction from baseline) after 9 months of treatment.

FABHALTA REMS

Because of the risk of serious infections, Fabhalta is available only through a restricted program under a REMS. Under the FABHALTA REMS, prescribers must enroll in the program. Prescribers must counsel patients about the risk of serious infection, provide the patients with the REMS educational materials, instruct patients to always carry the Patient Safety Card with them during and 2 weeks following treatment with Fabhalta, and ensure patients are vaccinated against encapsulated bacteria per ACIP recommendations directed by the prescriber prior to treatment with Fabhalta. Patients must receive antibiotics as directed by the prescriber if they are not up to date on vaccinations against encapsulated bacteria and have to start Fabhalta right away. Enrollment in the FABHALTA REMS and additional

information are available by telephone: 1-833-993-2242 or at www.fabhalta-rems.com

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Fabhalta (iptacopan) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Fabhalta (iptacopan) include: serious hypersensitivity to iptacopan or any of the excipients, initiation in patients with unresolved serious infection caused by encapsulated bacteria.

Healthcare providers should monitor for signs of hemolysis for at least 2 weeks following discontinuation of Fabhalta. The signs included are elevated lactate dehydrogenase (LDH) levels along with a sudden decrease in hemoglobin or PNH clone size, fatigue, hemoglobinuria, abdominal pain, dyspnea, major adverse vascular events (such as thrombosis, stroke and myocardial infarction), dysphagia, or erectile dysfunction. The increased risk of a serious infection may continue for a few weeks after the last dose Fabhalta. Inform patients who discontinue Fabhalta to keep the Patient Safety Card with them for 2 weeks after the last dose of Fabhalta.

OTHER SPECIAL CONSIDERATIONS:
Fabhalta (iptacopan) has a Black Box Warning for serious infections caused by encapsulated bacteria: Meningococcal infections may occur in patients treated with FABHALTA and may become rapidly life-threatening or fatal if not recognized and treated early. Use of FABHALTA may predispose individuals to serious infections, especially those caused by encapsulated bacteria, such as *Streptococcus pneumoniae*, *Neisseria meningitidis (serogroups A, C, W, Y and B)*, and *Haemophilus influenzae* type B. Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against encapsulated bacteria. Vaccinate patients against encapsulated bacteria as recommended at least 2 weeks prior to administering the first dose of FABHALTA unless the risks of delaying FABHALTA therapy outweigh the risks of developing a serious infection. Vaccination reduces, but does not eliminate, the risk of serious infections. Monitor patients for early signs of serious infections and evaluate immediately if infection is suspected.

Fabhalta adherence to dosing schedule as prescribed is important to minimize hemolysis risk. If a dose or doses are missed, administer one iptacopan dose as soon as possible (even if it is soon before the next scheduled dose) and then resume the regular dosing schedule. Fabhalta can be administered without regard to food. Swallow whole; do not open, break, or chew capsules.

To reduce the potential risk of hemolysis with abrupt discontinuation of other PNH therapies: for patients switching from eculizumab, initiate Fabhalta no later than 1 week after the last dose of eculizumab; for patients switching from ravulizumab, initiate Fabhalta no later than 6 weeks after the last dose of ravulizumab. There is no available information regarding the timeframe for initiation of Fabhalta after other PNH therapies.

Fabhalta increases total cholesterol, LDL-cholesterol, and serum triglycerides. Monitor serum lipid parameters periodically during treatment and initiate cholesterol-lowering medication, if indicated. The efficacy of Fabhalta can be decreased with concomitant use of CYP2C8 inducers. Monitor for loss of efficacy of Fabhalta. Safety and effectiveness in pediatric patients have not been established. It is not known if Fabhalta is present in breastmilk. Breastfeeding is not recommended by the manufacturer during therapy and for 5 days after the last dose of Fabhalta.

CODING/BILLING INFORMATION

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the*

American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Fabhalta CAPS 200MG

REFERENCES

1. Fabhalta (iptacopan) capsule [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; August 2024.
2. Bektas, M., Copley-Merriman, C., Khan, S., Sarda, S.P., & Shammo, J.M. (2020). Paroxysmal nocturnal hemoglobinuria: Patient Journey and Burden of Disease. *Journal of Managed Care & Specialty Pharmacy, 26*(12-b Suppl), S8-S14. https://doi.org/10.18553/jmcp.2020.26.12-b.s8
3. Hill, A., Platts, P.J., Smith, A., Richards, S.J., Cullen, M.J., Hill, Q.A., Roman, E., & Hillmen, P. (2006). The Incidence and Prevalence of Paroxysmal Nocturnal Hemoglobinuria (PNH) and Survival of patients in Yorkshire. *Blood, 108*(11),985-985. https://doi.org/10.1182/blood.v108.11.985.985
4. Novartis Pharmaceuticals Corporation. Study to evaluate the efficacy and safety of twice daily oral LNP023 in adult PNH patients with residual anemia despite anti-c5 antibody treatment. www.clinicaltrials.gov/study/NCT04558918. NLM identifier: NCT04558918.
5. Novartis Pharmaceuticals Corporation. Study to evaluate the efficacy and safety of twice daily oral iptacopan (LNP023) in adult PNH patients who are naïve to complement inhibitor therapy. www.clinicaltrials.gov/study/NCT04820530. NLM identifier: NCT04820530.
6. Brodsky, R. A. (2024). Not So Benign Paroxysmal Nocturnal Hemoglobinuria: Many Targets, Many Drugs. The Hematologist, 21(2). https://doi.org/10.1182/hem.v21.2.202428
7. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int. 2021;100(4S):S1–S276.
8. Lv, J., Wong, M. G., Hladunewich, M. A., Jha, V., Hooi, L. S., Monaghan, H., Zhao, M., Barbour, S., Jardine, M. J., Reich, H. N., Cattran, D., Glassock, R., Levin, A., Wheeler, D. C., Woodward, M., Billot, L., Stepien, S., Rogers, K., Chan, T. M., Liu, Z. H., … TESTING Study Group (2022). Effect of Oral Methylprednisolone on Decline in Kidney Function or Kidney Failure in Patients With IgA Nephropathy: The TESTING Randomized Clinical Trial. JAMA, 327(19), 1888–1898. https://doi.org/10.1001/jama.2022.5368
9. Caravaca-Fontán, F., Gutiérrez, E., Sevillano, Á. M., & Praga, M. (2023). Targeting complement in IgA nephropathy. Clinical Kidney Journal, 16(Supplement_2), ii28–ii39. https://doi.org/10.1093/ckj/sfad198

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Diagnosis Required Medical Information Continuation of Therapy Prescriber Requirements FDA-Approved Uses Background References	Q4 2024

REVISION- Notable revisions: Required Medical Information Prescriber Requirements Contraindications/Exclusions/Discontinuation References	Q3 2024
NEW CRITERIA CREATION	Q2 2024