Policy Number	**RX501.176**
Policy Effective Date	**10/15/2025**

Crovalimab-akkz

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Crovalimab-akkz (Piasky) **may be considered medically necessary** to reduce hemolysis in individuals 13 years and older who are at least 40 kilograms (kg) who have paroxysmal nocturnal hemoglobinuria (PNH) AND meet the following criteria:

- Documentation of diagnosis of PNH through analysis by:
    - Flow cytometry of erythrocytes for CD59 deficiency; or
    - Granulocytes for either CD59 or CD55; AND
- Will not receive concurrently with other biologics used to treat PNH (e.g., ravulizumab, eculizumab).

Crovalimab-akkz (Piasky) **is considered experimental, investigational and/or unproven** for all other non-Food and Drug Administration approved indications.

Policy Guidelines

Piasky is available only through a restricted Risk Evaluation and Mitigation Strategy (REMS) program called Piasky REMS.

Description

Paroxysmal nocturnal hemoglobinuria (PNH)
PNH is a chronic, progressive, debilitating, and life-threatening ultra-rare blood disorder that is characterized by the destruction of red blood cells. PNH is caused by a mutation in the X-linked PIGA gene, whose product is required for the first step in glycophosphatidylinositol (GPI) anchor synthesis. This acquired mutation occurs in a hematopoietic stem cell and leads to the expansion of stem cells with severely deficient or absent GPI. The absence of GPI-anchored proteins, CD55 and CD59, account for most of the clinical manifestations of PNH. CD55 and CD59 are regulatory proteins that normally bind to surface proteins and protect red blood cells from the complement system. The absence of these proteins leads to immune-mediated destruction of red blood cells. (2)

Symptoms may vary widely and can include fatigue, difficulty swallowing, shortness of breath, abdominal pain, erectile dysfunction, hemoglobinuria, and anemia. Complications of PNH include bone marrow failure, renal failure, pulmonary hypertension, and thrombosis in blood vessels throughout the body which can result in organ damage or even death. (3)

PNH is a rare disease with a worldwide incidence estimated at 1.3 cases per million population. The onset of PNH is typically in adults, with pediatric cases accounting for only 5-10% of reported cases. (4)

Crovalimab-akkz (Piasky) is a monoclonal antibody that specifically binds with high affinity to the complement protein C5, inhibiting its cleavage into C5a and C5b, preventing the formation of the membrane attack complex (MAC). Crovalimab-akkz inhibits terminal complement-mediated intravascular hemolysis in patients with PNH. (1)

Regulatory Status
In 2024, the U.S. Food and Drug Administration (FDA) approved crovalimab-akkz (Piasky) for the treatment of adult and pediatric patients 13 years and older with paroxysmal nocturnal hemoglobinuria (PNH) and body weight of at least 40 kg. (1)

Rationale

This policy is based on the U.S. Food and Drug Administration (FDA) labeled indications for crovalimab-akkz (Piasky) and a specialty society guideline.

Crovalimab-akkz (Piasky) (1)
The efficacy of Piasky in patients with paroxysmal nocturnal hemoglobinuria (PNH) was evaluated in COMMODORE 2 (NCT04434092), an active-controlled, open-label, non-inferiority study that randomized 204 patients (body weight ≥ 40 kg) with PNH not previously treated with a complement inhibitor in a 2:1 ratio to receive either Piasky (n=135) or eculizumab (n=69). The study additionally enrolled 6 pediatric patients (aged >12 years and body weight ≥ 40 kg) to receive Piasky in a separate non-randomized cohort.

Patients were required to be vaccinated against *Neisseria meningitidis*, either within 3 years prior to the start of treatment or within 7 days after starting treatment with Piasky. Patients vaccinated within 2 weeks prior to initiating Piasky or after the start of study treatment received prophylactic antibiotics until at least 2 weeks after the vaccination.

A single intravenous loading dose of Piasky was given on Day 1 (1,000 mg for patients weighing ≥40 kg to <100 kg, or 1,500 mg for patients weighing >100 kg), followed by four additional weekly subcutaneous loading doses of 340 mg on Days 2, 8, 15 and 22. Starting at Day 29, maintenance subcutaneous doses were given every 4 weeks (680 mg for patients weighing ≥40 kg to <100 kg, or 1,020 mg for patients weighing ≥100 kg).

The study consisted of a primary treatment period of 24 weeks, after which patients had the option to continue or switch to Piasky in an extension period.

Eligible patients had lactate dehydrogenase (LDH) level ≥ 2 x upper limit of normal (ULN) and at least one or more PNH-related signs or symptoms in the past 3 months. Randomization was

stratified by the most recent LDH value (≥ 2 to ≤ 4 × ULN, or > 4 × ULN) and by the transfusion history (0, > 0 to ≤ 6, or > 6 packed red blood cell [pRBC] units administered within 6 months prior to randomization). In the Piasky and eculizumab arms, the median PNH clone size was 90.9% and 95.1% for monocytes, 91.4% and 93.6% for granulocytes, and 25.3% and 44.6% for erythrocytes, respectively.

Demographics and baseline characteristics of the randomized study population were generally balanced between the treatment arms.

Efficacy was based on hemolysis control, as measured by the mean proportion of patients with LDH ≤ 1.5 x ULN from Week 5 to Week 25; and the proportion of patients who achieved transfusion avoidance, defined as patients who were pRBC transfusion-free, from baseline through Week 25. Other efficacy endpoints included the proportion of patients with breakthrough hemolysis and the proportion of patients with stabilized hemoglobin. Breakthrough hemolysis was defined as at least one new or worsening symptom or sign of intravascular hemolysis in the presence of elevated LDH ≥ 2 x ULN after prior reduction of LDH to ≤ 1.5 x ULN on treatment. Hemoglobin stabilization was defined as avoidance of a ≥ 2 g/dL decrease in hemoglobin level from baseline, in the absence of transfusion.

Pediatric Population with PNH Treated with Piasky

Efficacy was evaluated in 12 pediatric patients (with body weight ≥ 40 kg) treated with Piasky in COMMODORE 2 (n=7; 13-17 years old), COMMODORE 1 (n=2; 13-16 years old) and in a single arm study in patients who were complement-inhibitor naïve, COMMODORE 3 (NCT04654468; n=3; 15-17 years old).

Nine pediatric patients were treatment-naïve, two patients switched from standard dose eculizumab, and one patient switched from ravulizumab. Six pediatric patients were females and six were males. Nine patients were Asian, two were White and for one pediatric patient the race was unknown. The proportion of patients with a history of transfusions in the prior 12 months was 58%, with a median number of 1.3 pRBC units (range: 0-40.5) transfused, and a baseline median LDH of 6.4 x ULN (range 1.1-26.6). Aplastic anemia was reported in 50% of patients. All pediatric patients received the same dosing as adult patients based on body weight. Hemolysis control (defined as LDH ≤ 1.5 x ULN) from baseline to Week 25 was achieved in 7 of the 9 patients who were treatment-naïve, and the 3 patients switching from eculizumab or ravulizumab to Piasky maintained hemolysis control through 24 weeks of Piasky treatment. Nine (six patients who were treatment-naïve and three patients who switched from eculizumab or ravulizumab) out of the 12 pediatric patients achieved transfusion avoidance and hemoglobin stabilization, and no patients had a breakthrough hemolysis event during the 24-week treatment period.

Overall, the treatment effect of Piasky in pediatric patients with PNH was consistent with that observed in adults with PNH.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J1307

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

U.S. Food and Drug Administration Label:

1. U.S. Food and Drug Administration, Drugs@FDA. Highlights of Prescribing Information: Piasky (crovalimab-akkz) (June 2024). Available at <https://www.accessdata.fda.gov> (accessed July 31, 2025).

Other:

2. Bessler M and J Hiken. The pathophysiology of disease in patients with paroxysmal nocturnal hemoglobinuria. Hematology Am Soc Hematol Educ Program. 2008; 2008(1):104-110. PMID 19074066
3. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. Blood. 2014; 124(18):2804–2811. PMID 25237200
4. Urbano-Ispizua A, Muus P, Schrezenmeier H, et al. Different clinical characteristics of paroxysmal nocturnal hemoglobinuria in pediatric and adult patients. Haematologica. Mar 2017; 102(3):e76-e79. PMID 27884975
5. Parker C, Omine M, Richards S, et al. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. For the International PNH Interest Group. Blood. Jul 28 2005; 106(12):3699-3709. PMID 16051736

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
10/15/2025	Document updated with literature review. The following change was made to Coverage: Added “for all other non-Food and Drug Administration approved” to experimental, investigational and/or unproven statement. Reference 5 added.
03/15/2025	New medical document. Crovalimab-akkz (Piasky) may be considered medically necessary to reduce hemolysis in individuals 13 years and older who are at least 40 kg who have paroxysmal nocturnal hemoglobinuria (PNH) AND meet the criteria noted in Coverage. Crovalimab-akkz (Piasky) is considered experimental, investigational and/or unproven for all other indications.