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Policy Number: C28638-A

PiaSky (crovalimab)

PRODUCTS AFFECTED

PiaSky (crovalimab)

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)

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. Documented diagnosis of Paroxysmal nocturnal hemoglobinuria (PNH)

AND

2. Prescriber attests that member has been vaccinated against meningococcal infection (serogroups A, C, W, Y, and B) at least 2 weeks prior to treatment, if not previously vaccinated.
AND
3. Documentation of baseline labs and status [DOCUMENTATION REQUIRED]:
   a. Hemoglobin level
   AND
   b. Documentation of Lactate dehydrogenase (LDH) 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 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 (1) month since last transfusion)

AND

4. 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 PiaSky (crovalimab) include: Initiation during unresolved serious Neisseria meningitidis infection, Patients who are not currently vaccinated against Neisseria meningitidis, unless the risks of delaying treatment outweigh the risks of developing a meningococcal infection, serious hypersensitivity to crovalimab or any of the excipients.]

AND

5. Documentation member meets ONE of the following: 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

CONTINUATION OF THERAPY:

A. PAROXYSMAL NOCTURNAL HEMOGLOBINURIA:
   1. 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
   AND
   2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

DURATION OF APPROVAL:

Initial authorization: 6 months; Continuation of therapy: 12 months

PRESCRIBER REQUIREMENTS:

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

AGE RESTRICTIONS:

13 years of age and older

QUANTITY:

Loading dose:

≥*40 kg to <100 kg:* 1,000 mg IV on day 1, then 340 mg SUBQ on days 2, 8, 15, and 22

≥*100kg:* 1,500 mg IV on day 1, then 340 mg SUBQ on days 2, 8, 15, and 22.

Maintenance dose:
≥40 kg to <100 kg: SUBQ: 680 mg on day 29 and then every 4 weeks thereafter
≥100 kg: SUBQ: 1,020 mg on day 29 and then every 4 weeks thereafter

PLACE OF ADMINISTRATION:
The recommendation is that infused medications in this policy will be for pharmacy or medical benefit coverage administered in a place of service that is a non-hospital facility-based location as per the Molina Health Care Site of Care program.

Note: Site of Care Utilization Management Policy applies for PiaSky (crovalimab). For information on site of care, see Specialty Medication Administration Site of Care Coverage Criteria (molinamarketplace.com)

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Intravenous, Subcutaneous

DRUG CLASS:
Complement C5 Inhibitor

FDA-APPROVED USES:
Indicated 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

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 (crovalimab), and potential curative treatment (allogeneic bone marrow transplantation).

PiaSky (crovalimab) is a monoclonal antibody that targets complement C5 inhibition. This further prevents the membrane attack complex formation and ultimately inhibits hemolysis in PNH patients.

PiaSky is available in a subcutaneous injection formulation, which differentiates it from other complement C5 inhibitors which are administered by intravenous infusion.

Clinical Studies

Phase 3 randomized COMMODORE 1 trial: Crovalimab versus eculizumab in complement inhibitor-experienced patients with paroxysmal nocturnal hemoglobinuria

Study population: Inclusion: Adult patients ≥40kg with a PNH diagnosis confirmed by high-sensitivity flow cytometry, with granulocyte or monocyte GPI-deficient clone size ≥10%. Patients must have a lactate dehydrogenase level ≤1.5X the ULN at screening and who have been treated with eculizumab 900 mg every 2 weeks for ≥ 24 weeks prior. All patients must have a platelet count of >30,000/mm^3 and an absolute neutrophil count of >500/mm^3. Exclusion: Major adverse vascular event in the 6 months prior or a history of *Neisseria meningitidis* infection within 6 months prior to screening and up to the first study drug administration.

Phase, Study Design, Sample Size: A global, randomized, open-label, multicenter, phase 3 trial evaluating crovalimab vs. Eculizumab in patient with PNH who had adequately controlled intravascular hemolysis on approved eculizumab dosing. The study started with a 4-week screening period followed by a 24-week primary treatment period with patients randomized 1:1 to crovalimab or eculizumab. Next was an extension period where patients could continue crovalimab or switch from eculizumab to crovalimab. Lastly if patients discontinued the treatment at any time, they entered a safety follow-up period. Sample size- 89 patients with 45 randomized to the crovalimab arm and 44 randomized to the eculizumab arm.

Outcomes: Due to developments in treatment options and a limited number of patients being treated with eculizumab for the required ≥24 weeks prior to the study, this study was unable to be properly powered for efficacy analyses and therefore all planned efficacy endpoints became exploratory with safety becoming the new primary objective. Of the initial study population, only 44 receiving crovalimab and 42 receiving eculizumab were eligible to be included in the evaluation of safety. Patients were assessed on adverse reactions, infection rates, and transient immune complex reactions. 77% of participants in the crovalimab group compared to 67% of those on eculizumab did experience ≥1 adverse event with the most common reaction (≥5%) being fever (16% with crovalimab vs. 2% with eculizumab), COVID-19 (14% vs 17%) and infusion related headaches (14% vs 0%). Looking at infection rates, crovalimab saw a slightly higher incidence (41%) than eculizumab (36%) with nasopharyngitis (n=1), pneumonia (n=1), pyelonephritis (n=1), and urinary tract infections (n=1) being the most serious infections seen during the trial with zero reported occurrences of meningococcal infections in either group. All serious infections were considered unrelated to the treatment by the investigator. Lastly, those in the crovalimab group who had previously taken eculizumab showed a 16% incidence of transient immune complex reactions also known as Type III hypersensitivity. This was an expected risk for those switching between C5 inhibitors that bind to different C5 epitopes such as crovalimab and eculizumab. The most common manifestations of transient immune complex reactions were rash (11%), arthralgia and/or myalgia (11%). All transient immune complex reactions resolved with no change in crovalimab treatment. Overall, COMMODORE 1 showed that crovalimab was well tolerated in patients switching from eculizumab to crovalimab for treatment of PNH.

Phase 3 randomized COMMODORE 2 trial: Crovalimab versus eculizumab in patients with paroxysmal nocturnal hemoglobinuria naive to complement inhibition

Study population: Inclusion: Adult patients ≥40kg with a PNH diagnosis confirmed by high-sensitivity flow cytometry, with granulocyte or monocyte GPI-deficient clone size ≥10%. Patients must also have a clinically significant disease activity at screening demonstrated by a lactate dehydrogenase level ≥2X ULN and the presence of one or more PNH-related signs or symptoms in the past 3 months. Exclusion: Current or previous treatment with complement inhibitor or *Neisseria meningitidis* infection within the past 6 months.

Phase, Study Design, Sample Size: Phase 3, randomized, open-label, active-controlled study investigating crovalimab vs. Eculizumab in adult patients (≥18 years old). A second descriptive, non-randomized arm explored crovalimab in pediatric patients (<18 years old) but that arm was not detailed in the clinical trial

journal publication. In the adult arm of this trial, patients were randomized 2:1 to receive either crovalimab or eculizumab. The study consisted of a 4-week screening period followed by a 24-week primary treatment period. Next was an extension period where patients could either continue crovalimab or switch to crovalimab if they were being treated with eculizumab. Sample size- 204 patients were randomized with 135 receiving crovalimab and 69 receiving eculizumab.

Outcomes: The primary objective of this study was to assess efficacy and the non-inferiority of crovalimab compared with eculizumab by looking at two primary endpoints: hemolysis control and transfusion avoidance. Crovalimab was concluded to be non-inferior to eculizumab for both primary endpoints. The mean proportion of patients with hemolysis control was 79.3% for crovalimab and 79% for eculizumab. The estimated OR for comparison of crovalimab vs eculizumab was 1.0(95% CI: 0.6, 1.8). For the endpoint of transfusion avoidance 65.7% of crovalimab patients and 68.1% of eculizumab patients achieved transfusion avoidance. The weighted difference in proportion of patients achieving transfusion avoidance between the crovalimab and eculizumab arm was 2.8% (95% CI: -15.7, 11.1). Overall, COMMODORE 2 showed that crovalimab had a similar safety profile when compared to eculizumab.

PiaSky REMS

PIASKY is available only through a restricted program under a REMS called PIASKY REMS, because of the risk of serious meningococcal infections.

Notable requirements of the PIASKY REMS include the following:

- Prescribers must enroll in the REMS.
- Prescribers must counsel patients about the risk of serious meningococcal infection.
- Prescribers must provide the patients with the REMS educational materials.
- Prescribers must assess patient vaccination status for meningococcal vaccines (against serogroups A, C, W, Y, and B) and vaccinate if needed according to current ACIP recommendations two weeks prior to the first dose of PIASKY.
- Prescribers must provide a prescription for antibacterial drug prophylaxis if treatment must be started urgently, and the patient is not up to date with both meningococcal vaccines according to current ACIP recommendations at least two weeks prior to the first dose of PIASKY.
- Healthcare settings and pharmacies that dispense PIASKY must be certified in the REMS and must verify prescribers are certified.
- Patients must receive counseling from the prescriber about the need to receive meningococcal vaccines per ACIP recommendations, the need to take antibiotics as directed by the prescriber, and the signs and symptoms of meningococcal infection.
- Patients must be instructed to carry the Patient Safety Card with them at all times during and for 11 months following treatment with PIASKY.

Further information is available at www.PIASKYREMS.com or 1-866-4My-Skyy (469-7599).

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of PiaSky (crovalimab) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to PiaSky (crovalimab) include: initiation during unresolved serious Neisseria meningitidis infection, Patients who are not currently vaccinated against Neisseria meningitidis, unless the risks of delaying treatment outweigh the risks of developing a meningococcal infection, serious hypersensitivity crovalimab or any of the excipients.

OTHER SPECIAL CONSIDERATIONS:

PiaSky (crovalimab) has a Black Box Warning for serious meningococcal infection. Life- threatening and fatal meningococcal infections have occurred in patients treated with crovalimab. Meningococcal infection may become rapidly life- threatening or fatal if not recognized and treated early.

PiaSky (crovalimab) has an increased risk of Type III hypersensitivity in patients switching from another

C5 inhibitor to PiaSky or from PiaSky to another C5 inhibitor due to the formation of drug- target- drug complexes

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
J3590	Unclassified biologic (PiaSky)

AVAILABLE DOSAGE FORMS:
PiaSky SOLN 340MG/2ML single-dose vial

REFERENCES

1. PiaSky (crovalimab-akkz) injection, for intravenous or subcutaneous use [prescribing information]. San Fransico, CA: Genentech, Inc; June 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. 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. Röth A, He G, Tong H, et al. Phase 3 randomized COMMODORE 2 trial: Crovalimab versus eculizumab in patients with paroxysmal nocturnal hemoglobinuria naive to complement inhibition. *Am J Hematol*. 2024;99(9):1768-1777. doi:10.1002/ajh.27412
5. Scheinberg P, Clé DV, Kim JS, et al. Phase 3 randomized COMMODORE 1 trial: Crovalimab versus eculizumab in complement inhibitor-experienced patients with paroxysmal nocturnal hemoglobinuria. *Am J Hematol*. 2024;99(9):1757-1767. doi:10.1002/ajh.27413

SUMMARY OF REVIEW/REVISIONS	DATE
NEW CRITERIA CREATION	Q4 2024