LOUISIANA BLUE

crovalimab-akkz (PiaSky®)

Policy # 00903
Original Effective Date: 12/01/2024
Current Effective Date: 12/01/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider crovalimab-akkz (PiaSky®)‡ for the treatment of paroxysmal nocturnal hemoglobinuria to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for crovalimab-akkz (PiaSky) for the treatment of paroxysmal nocturnal hemoglobinuria will be considered when the following criteria are met:

- Initial
    - Patient has received vaccination against meningococcal infections within 2 years prior to, or at the time of initiating the requested drug; AND
    - If the drug is initiated < 2 weeks after meningococcal vaccination, patient will receive prophylactic antibiotics until 2 weeks after vaccination; AND
    - Patient is 13 years of age or older; AND
    - Patient weight is ≥ 40 kg; AND
    - Documentation is provided of peripheral blood high sensitivity flow cytometry results showing a granulocyte or monocyte clone size of ≥ 5%; AND
    - Patient meets ONE of the following (i or ii):
        i. Patient has at least ONE of the following significant disease manifestations caused by hemolysis (a, b, c, d, OR e):
            a. Documented history of a major adverse vascular event (MAVE) from thromboembolism; OR
            b. Presence of organ damage secondary to chronic hemolysis (e.g., worsening renal insufficiency); OR
            c. Patient is transfusion-dependent as evidenced by 2 or more transfusions in the 12 months prior to initiation of treatment; OR

d. Patient has a high lactate dehydrogenase (LDH) activity defined as ≥ 1.5 times the upper limit of normal with clinical symptoms (e.g., severe fatigue, dyspnea, jaundice, abdominal or chest pain, discolored urine, dysphagia, pulmonary hypertension); OR
e. Patient has symptomatic anemia with a hemoglobin less than the lower limit of normal; OR

ii. Patient has been previously receiving eculizumab (Soliris®)‡, ravulizumab (Ultomiris™)‡, pegcetacoplan (Empaveli™)‡, or iptacopan (Fabhalta®)‡ for the treatment of PNH and is switching to PiaSky; AND
*(Note: These specific patient selection criteria are additional Company requirements for coverage eligibility and will be denied as not medically necessary** if not met.)*

- For a patient transitioning to PiaSky from Soliris, Ultomiris, Empaveli, or Fabhalta, the prescriber attests that these medications will be discontinued within 4 weeks after starting PiaSky; AND
- PiaSky will not be used in combination with danicopan (Voydeya™)‡; AND
- The requested dose is less than or equal to 1,500 mg via intravenous infusion on day 1 followed by 340 mg subcutaneous injection on days 2, 8, 15, and 22 followed by 1,020 mg on Day 29 and every 4 weeks thereafter

- Continuation
  - Patient has received an initial authorization for PiaSky; AND
  - Patient has experienced improvement on therapy as evidenced by at least ONE of the following:
    - Decreased serum LDH compared to pretreatment baseline; OR
    - Decreased need for blood transfusion compared to pretreatment baseline; OR
    - Stabilization of hemoglobin; AND
      *(Note: These specific patient selection criteria are additional Company requirements for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - PiaSky will not be used in combination with Soliris, Ultomiris, Empaveli, Fabhalta, or Voydeya; AND
  - The requested dose is less than or equal to 1,020 mg via subcutaneous injection every 4 weeks.

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When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of crovalimab-akkz (PiaSky) when the patient does not have a manifestation of significant disease or has not been previously receiving another disease modifying drug for PNH to be **not medically necessary.****

Based on review of available data, the Company considers the continued use of crovalimab-akkz (PiaSky) when the patient has not demonstrated improvement in PNH disease manifestations while on therapy to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of crovalimab-akkz (PiaSky) when the patient selection criteria are not met (except those noted to be **not medically necessary****) to be **investigational.***

Background/Overview

PiaSky is a complement inhibitor indicated for the treatment of patients 13 years of age and older with paroxysmal nocturnal hemoglobinuria (PNH) and a body weight of at least 40 kg. It is a monoclonal antibody that binds to the complement protein C5 and ultimately inhibits terminal complement-mediated intravascular hemolysis in patients with PNH. Dosing is weight-based and initiated via an intravenous infusion followed by 4 weekly subcutaneous injections. The maintenance dose starts on Day 29 and is then administered every 4 weeks by subcutaneous injection. All doses of PiaSky must be administered by a healthcare provider.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

PNH is an acquired hematopoietic stem cell disorder associated with an acquired somatic mutation of the phosphatidylinositol glycan class A (*PIGA*) gene. Mutations disrupt the first step in glycophosphatidylinositol (GPI) synthesis, which causes an absence of the GPI anchor and a deficiency of GPI proteins. The absence of GPI proteins on erythrocytes makes them susceptible to attack by complement and intravascular hemolysis. Intravascular hemolysis associated with PNH leads to release of free hemoglobin, leading to anemia, hemoglobinuria, thrombosis, dysphagia, abdominal pain, pulmonary hypertension, renal impairment, and erectile dysfunction. The prevalence of PNH is estimated to be between 0.5-1.5 per million people in the general population, with an approximately equal male to female distribution. Although PNH can affect any age group, the median age at diagnosis is during the fourth decade of life. The primary clinical finding is hemolysis of red blood cells by complement, which leads to hemoglobinuria that is most prominent in the morning. Those with PNH are also susceptible to repeated, potentially life-threatening thromboses. Underlying bone marrow dysfunction may also be present and those who are severely

affected may have pancytopenia. Many patients also have acquired aplastic anemia. Although less common, some patients have concomitant myelodysplasia. For unknown reasons, PNH may rarely develop into acute leukemia.

Signs and symptoms of PNH may vary with some patients exhibiting mild and stable disease for many years while other patients have severe symptoms that rapidly progress to life-threatening. However, chronic hemolysis is central to all of the symptoms and physical findings associated with PNH. Fatigue, rapid heartbeat, headaches, and chest pain and difficulty breathing while exercising can result from mild hemolysis. With severe hemolysis, disabling fatigue, dysphagia, and painful contractions of the abdomen and esophagus may occur. It is estimated that 15-30% of patients with PNH develop blood clots, particularly venous thrombosis. Diagnosis of PNH is suspected in those with unexplained hemoglobinuria or abnormally high serum lactate dehydrogenase (LDH) levels. However, flow cytometry is the main diagnostic test for the identification of PNH cells.

The only curative treatment for PNH is allogeneic hematopoietic stem cell transplant, but this is associated with significant morbidity and mortality and is typically only recommended for patients with severe bone marrow failure. The current standard of care treatments include the complement C5 inhibitor products ravulizumab (Ultomiris) and eculizumab (Soliris). Approximately 10-20% of patients treated with a C5 inhibitor experience clinically significant extravascular hemolysis which can result in continued symptoms of anemia and require blood transfusions. Additional newer treatment options for this condition include pegcetacoplan (Empaveli), a self-administered subcutaneous complement C3 inhibitor; iptacopan (Fabhalta), an oral selective inhibitor of complement factor B; and danicopan (Voydeya), a factor D inhibitor given orally in addition to Soliris or Ultomiris.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

PiaSky was approved in June 2024 for the treatment of adult and pediatric patients 13 years of age and older with paroxysmal nocturnal hemoglobinuria (PNH) and body weight of at least 40 kg.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The efficacy of PiaSky in patients with PNH was evaluated in COMMODORE 2, 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.

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 LDH level ≥ 2 times the 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 and by the transfusion history. 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 22.6% for erythrocytes respectively.

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. In the PiaSky group, 79.3% of patients achieved hemolysis control compared to 79.0% in the eculizumab group (Odds ratio of 1.02 [95% CI 0.57, 1.82]). Transfusion avoidance was achieved by 65.7% in the PiaSky group and 68.1% in the eculizumab group (-2.8% difference [95% CI -15.7, 11.1]).

References

1. PiaSky [package insert]. Genentech, Inc. South San Francisco, CA. Updated June 2024.
2. PiaSky New Drug Review. IPD Analytics. Updated August 2024.

Policy History

Original Effective Date: 12/01/2024
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11/07/2024 Medical Policy Committee review
11/13/2024 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 11/2025

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Coding

The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2023 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J3490, J3590, C9399
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.