LOUISIANA BLUE

mitapivat (Pyrukynd®)

Policy # 00799
Original Effective Date: 07/11/2022
Current Effective Date: 07/01/2025

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 mitapivat (Pyrukynd®)‡ for the treatment of hemolytic anemia associated with pyruvate kinase deficiency to be **eligible for coverage.****

Patient Selection Criteria
Coverage eligibility for mitapivat (Pyrukynd) will be considered when the following criteria are met:

- **Initial** (6 months)
  - Patient is ≥18 years of age; AND
  - Patient has a diagnosis of pyruvate kinase deficiency established by BOTH of the following (documentation of genetic testing required):
    - Presence of at least two variant/mutant alleles in the pyruvate kinase liver and red blood cell (*PKLR*) gene; AND
    - At least one of the variant/mutant alleles was a missense variant; AND

    *(Note: These specific patient criteria are additional Company requirements for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - Patient has a diagnosis of hemolytic anemia associated with pyruvate kinase deficiency.
  - Patient is not homozygous for the p.R479H mutation in the *PKLR* gene; AND
    *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - Patient has a current hemoglobin level ≤10 g/dL.
    *(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- **Continuation** (1 year)
  - Patient has received an initial authorization for Pyrukynd; AND
  - Patient has experienced improvement while on therapy as evidenced by at least ONE of the following:
    - Increase in Hb≥1.5 g/dL over baseline; OR

- Reduction in transfusion burden; OR
- Improvement in or maintenance of hemolysis laboratory parameters (e.g., indirect bilirubin, LDH, and haptoglobin).

*(Note: These specific patient criteria are additional Company requirements for coverage eligibility and will be denied as not medically necessary** if not met.)*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of mitapivat (Pyrukynd) when the patient's diagnosis was not established by at least two variant alleles in the *PKLR* gene with at least one missense variant or if the patient is homozygous for the p.R479H mutation in the *PKLR* gene to be **not medically necessary.****

Based on review of available data, the Company considers the initial use of mitapivat (Pyrukynd) when the patient's hemoglobin is greater than 10 g/dL to be **not medically necessary.****

Based on review of available data, the Company considers the continued use of mitapivat (Pyrukynd) when the patient has not experienced improvement 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 mitapivat (Pyrukynd) when the patient selection criteria are not met (except those noted to be **not medically necessary**)** to be **investigational.***

Background/Overview

Pyrukynd is a pyruvate kinase activator indicated for the treatment of hemolytic anemia in adults with pyruvate kinase deficiency. It acts by binding to the pyruvate kinase tetramer to increase pyruvate kinase activity and is the first treatment approved that targets the underlying mechanism of the disease. The recommended starting dose of Pyrukynd is 5 mg by mouth twice daily with a gradual increase to the recommended dose of 50 mg twice daily. Hemoglobin levels and transfusion requirements should be evaluated prior to each dose increase. Additionally, Pyrukynd should be discontinued if no benefit has been observed by 24 weeks as evaluated by hemoglobin and hemolysis laboratory results and transfusion requirements. Abrupt discontinuation should be avoided due to the risk of hemolysis, so the dose should be tapered gradually if the decision is made to discontinue therapy.

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Pyruvate kinase deficiency is a rare autosomal recessive genetic condition caused by mutations in the *PKLR* gene. It has an estimated prevalence of 3 to 9 cases per million people and affects both children and adults. The genetic mutations cause a reduction in pyruvate kinase activity in red blood cells which leads to hemolytic anemia of variable severity. The most common symptoms in adults are anemia, jaundice, scleral icterus, splenomegaly, fatigue, shortness of breath, and bone pain. Pyruvate kinase deficiency is also associated with serious complications that include pulmonary hypertension, extramedullary hematopoiesis, gallstones, and iron overload, which occur regardless of the degree of anemia or transfusion burden. Prior to the availability of Pyrukynd, management of the condition was supportive and included blood transfusions, splenectomy, and chelation therapy.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Pyrukynd was approved in February 2022 for the treatment of hemolytic anemia in adults with pyruvate kinase deficiency.

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 Pyrukynd in patients not regularly transfused was evaluated in ACTIVATE, a multinational, randomized, double-blind, placebo-controlled clinical study of 80 adults with pyruvate kinase deficiency who were not regularly transfused. Patients were included if they had no more than 4 transfusions in the 52-week period prior to treatment and no transfusions in the 3-month period prior to treatment, had documented presence of at least 2 variant alleles in the *PKLR* gene, of which at least 1 was a missense variant, and Hb less than or equal to 10 g/dL. Patients who were homozygous for the p.R479H variant or had 2 non-missense variants (without the presence of another missense variant) in the *PKLR* gene were excluded because these patients did not achieve Hb response (change from baseline in Hb$\geq$1.5 g/dL at >50% assessments) in the dose-ranging study. Among the 80 patients included in the study, 40 were randomized to Pyrukynd. Following a period of dose titration up to 50 mg twice daily, patients continued a fixed dose of Pyrukynd for 12 weeks. The majority (88%) of patients were maintained on 50 mg twice daily.

Efficacy was based upon Hb response, defined as a $\geq$1.5 g/dL increase in Hb from baseline sustained at 2 or more scheduled assessments (Weeks 16, 20, and 24) during the fixed dose period without transfusions. In the Pyrukynd group, 16 patients (40%) achieved a Hb response compared to 0 in the placebo group ($p<0.0001$). Of the 16 patients who responded, 15 patients continued in a long-term extension study and were evaluable for maintenance of response. Thirteen maintained increases in

Hb concentration from baseline above the response threshold of ≥1.5 g/dL at the last available Hb assessment without requiring any transfusions. The median duration of response for the 16 patients with Hb response was 6.9 months (range: 3.3, 18.4+).

The efficacy of Pyrukynd in patients with pyruvate kinase deficiency who were regularly transfused was evaluated in ACTIVATE-T, a multinational, single-arm trial of 27 adults with pyruvate kinase deficiency who had a minimum of 6 transfusion episodes in the 52-week period prior to informed consent. Patients were included if they had documented presence of at least 2 variant alleles in the *PKLR* gene, of which at least 1 was a missense variant. Patients who were homozygous for the p.R479H variant or had 2 non-missense variants (without the presence of another missense variant) in the *PKLR* gene were excluded. Following a period of dose titration up to 50 mg twice daily, patients continued on a fixed dose of Pyrukynd for 24 weeks.

Efficacy was based on transfusion reduction response and was defined as ≥33% reduction in the number of red blood cell (RBC) units transfused during the fixed dose period compared with the historical transfusion burden. Of the 27 patients treated with Pyrukynd, 9 (33%) experienced a transfusion reduction response and 6 (22%) were transfusion free at 24 weeks. Of the patients who were transfusion free, all 6 remained transfusion free in a long term extension study. The median duration of response for these 6 patients was 17 months (range: 11.5, 21.8).

References

1. Pyrukynd [package insert]. Agios Pharmaceuticals, Inc. Cambridge, MA. Updated February 2022.
2. Pyrukynd Drug Evaluation. Express Scripts. Updated March, 2022.

Policy History

Original Effective Date: 07/11/2022
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06/02/2022	Medical Policy Committee review
06/08/2022	Medical Policy Implementation Committee approval. New policy.
06/01/2023	Medical Policy Committee review
06/14/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/06/2024	Medical Policy Committee review
06/12/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/05/2025	Medical Policy Committee review
06/11/2025	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 06/2026

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*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.

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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.