PHARMACY COVERAGE GUIDELINE

PYRUKYND® (mitapivat) oral
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Pyrukynd (mitapivat) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Geneticist or Hematologist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of hemolytic anemia in pyruvate kinase (PK) deficiency by **ONE** of the following:
    a. Presence of at least 2 variant alleles in the pyruvate kinase liver and red blood cell (*PKLR*) gene, of which at least 1 is a missense variant

b. Measurement of low-level PK enzymatic activity in red blood cells

4. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
   a. Hemoglobin is less than 10 g/dL
   b. Documentation of 6 or more RBC transfusions due to PKD in the last year
   c. Liver tests

5. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. Individual does not have moderate or severe hepatic impairment

7. Individual does not have an estimated glomerular filtration rate of less than 30mL/min/1.73m^2

8. Individual does not have either of the following:
   a. Homozygous for the c.1436G>A (p.R479H) variant in the *PKLR* gene
   b. Two non-missense variants (without the presence of another missense variant) in the *PKLR* gene

9. There are no significant interacting drugs such as:
   a. Strong CYP3A inhibitors such as clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir, and others
   b. Strong CYP3A inducers such as rifampin phenobarbital, phenytoin, rifampicin, St. John's Wort and glucocorticoids, and others

Initial approval duration:
6 months
Continuation must show benefit in hemoglobin, hemolysis laboratory results and transfusion requirements

- **Criteria for continuation of coverage (renewal request):** Pyrukynd (mitapivat) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Geneticist or Hematologist

2. Individual's condition has responded while on therapy with response defined as **TWO** of the following:
   a. Hemoglobin is in the normal range or has increased by at least 1.5 g/dL from baseline
   b. Does not require transfusions or has at least a 33% decrease in the number of red blood cell units compared to historical transfusion use
   c. PK activity has increased by at least 10-fold over baseline
   d. Improvement or stabilization in markers for hemolysis (e.g., indirect bilirubin, lactate dehydrogenase, haptoglobin, etc.)

3. Individual has been adherent with the medication

4. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual does not have either of the following:
    a. Homozygous for the c.1436G>A (p.R479H) variant/mutation in the *PKLR* gene
    b. Two non-missense variants/mutations (without the presence of another missense variant/mutation) in the *PKLR* gene

6. Individual does not have moderate or severe hepatic impairment

7. Individual has not developed any significant adverse drug effect(s) that may exclude continued use such as hepatocellular injury

8. Individual does not have an estimated glomerular filtration rate of less than 30mL/min/1.73m^2

9. There are no significant interacting drugs as follows:
    a. Strong CYP3A inhibitors such as clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir, and others
    b. Strong CYP3A inducers such as rifampin phenobarbital, phenytoin, rifampicin, St. John's Wort and glucocorticoids, and others

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Description:

Pyrukynd (mitapivat) is indicated for the treatment of hemolytic anemia in adults with pyruvate kinase (PK) deficiency. Based on the hemoglobin, hemolysis laboratory results and transfusion requirements if no benefit has been observed by 24 weeks, discontinue Pyrukynd (mitapivat).

Mitapivat is a pyruvate kinase activator that acts by allosterically binding to the pyruvate kinase tetramer and increasing PK activity. The red blood cell (RBC) form of pyruvate kinase (PK-R) is mutated in PK deficiency, which leads to reduced adenosine triphosphate (ATP), shortened RBC lifespan, and chronic hemolysis.

PK deficiency is an inherited (autosomal recessive) RBC enzyme disorder that causes chronic hemolysis. Affected individuals are either homozygous for a single pathogenic mutation or compound heterozygous for two

different pathogenic variants affecting the function of the PK enzyme in RBCs and in the liver. The *PKLR* gene encodes the L (liver) and R (RBC) isoenzymes.

PK enzymes consist of several isoforms and are products of two distinct genes, PKLR and PKM both encoding enzymes that catalyze the transphosphorylation of phosphoenolpyruvate (PEP) into pyruvate and ATP during the terminal part of the glycolysis pathway. Clinical PK deficiency with hemolytic anemia is limited to mutations of the *PKLR* gene. There are more than 260 pathogenic variants reported for the *PKLR* gene. Testing for PK deficiency can be done by measuring PK activity in RBCs (biochemical testing) and/or by identifying a pathogenic *PKLR* gene mutation (genetic testing).

PK deficiency is the most common RBC enzyme defect causing chronic congenital non-spherocytic hemolytic anemia. The findings on the complete blood count (CBC) include normocytic anemia, an increased reticulocyte count, and an absence of specific RBC morphologic abnormalities on the peripheral blood smear. Other laboratory testing is consistent with a Coombs-negative hemolytic anemia. The severity of hemolysis seen, and the degree of the anemia is highly variable.

Some individuals with mild hemolysis due to PK deficiency may not be symptomatic. Those with more severe hemolysis may present with (or develop) pallor from severe anemia, icterus due to hemolysis, splenomegaly, gallstones that are pigment from bilirubin, folate deficiency, and skin ulcerations.

Treatment may include transfusions (if needed), folic acid, iron chelation for iron overload, splenectomy, and mitapivat to increase RBC PK activity.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Resources:

Pyrukynd (mitapivat) product information, revised by Agios Pharmaceutical, Inc. 01-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 18, 2025.

Prchal JT. Pyruvate kinase deficiency. In: UpToDate, Barcellini W, Tirnauer JS (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through February 2025. Topic last updated January 21, 2025. Accessed March 06, 2025.

DeBaun MR. Overview of hemolytic anemias in children. In: UpToDate, O'Brien S, Armsby C (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through February 2025. Topic last updated October 07, 2024. Accessed March 06, 2025.

Barcellini W. Diagnosis of hemolytic anemia in adults. In: UpToDate, Brodsky RA, Tirnauer JS (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through February 2025. Topic last updated June 21, 2024. Accessed March 06, 2025.

Al-Sankar H, Galacteros F, Glenthoj A, et. al.: Mitapivat versus Placebo for Pyruvate Kinase Deficiency. NEJM 2022 April 14; 386 (15):1432-1442. DOI: 10.1056/NEJMoa2116634. Accessed April 11, 2023. Re-evaluated March 06, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT NCT03548220: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of AG-348 in Not Regularly Transfused Adult Subjects With Pyruvate Kinase Deficiency. Available from: http://clinicaltrials.gov. Last update posted May 24, 2022. Last verified May 2022. Accessed April 11, 2023. Re-evaluated March 06, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT NCT03559699: An Open-Label Study To Evaluate the Efficacy and Safety of AG-348 in Regularly Transfused Adult Subjects With Pyruvate Kinase (PK) Deficiency. Available from: http://clinicaltrials.gov. Last update posted January 04, 2022. Last verified December 2021. Accessed April 11, 2023. Re-evaluated March 06, 2025.