BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 5/19/2022
LAST REVIEW DATE:
LAST CRITERIA REVISION DATE:
ARCHIVE DATE:

PYRUKYND® (mitapivat) oral

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy 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 BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

PYRUKYND® (mitapivat) oral

Criteria:

- **Criteria for initial therapy:** Pyrukynd (mitapivat) is considered ***medically necessary*** and will be approved when **ALL** of 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. 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 PK activity in red blood cells

  4. **ALL** of the following **baseline tests** have been completed before initiation of treatment with continued monitoring as clinically appropriate:
     a. Hemoglobin is less than 10 g/dL
     b. Number of transfusions is at least 4 transfusions per year

  5. Individual does not have moderate or severe hepatic impairment

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

  7. There are no significant interacting drugs
     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) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  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
     a. Response is defined as **TWO** of the following:
        i. Hemoglobin is in the normal range or has increased by at least 1.5 g/dL from baseline

PYRUKYND® (mitapivat) oral

ii. Does not require transfusions or has at least a 33% decrease in the number of red blood cell units compared to historical transfusion use
iii. PK activity has increased by at least 10-fold over baseline

3. Individual has been adherent with the medication

4. Individual has not developed any significant adverse drug effects that may exclude continued use
    a. Significant adverse effect such as:
        i. Acute hemolysis with subsequent anemia has been observed following abrupt interruption or discontinuation
        ii. Jaundice, scleral icterus, dark urine, dizziness, confusion, fatigue, or shortness of breath.

5. Individual does not have moderate or severe hepatic impairment

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

7. There are no significant interacting drugs
    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.

PYRUKYND® (mitapivat) oral

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.

Resources:

Pyrukynd (mitapivat) product information, revised by Agios Pharmaceutical, Inc. 02-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 09, 2022.

Prchal JT. Pyruvate kinase deficiency. In: UpToDate, Brodsky RA, Tirnauer JS (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated April 26, 2022. Accessed May 09, 2022.