Drug Coverage Policy

Effective Date.....06/15/2024
Coverage Policy Number.....IP0451
Policy Title..... Pyrukynd

Hematology – Pyrukynd

- Pyrukynd® (mitapivat tablets – Agios)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Cigna Healthcare Coverage Policy

OVERVIEW
Pyrukynd, a pyruvate kinase activator, is indicated for the treatment of **hemolytic anemia due to pyruvate kinase deficiency** in adults.[1]

It is recommended to discontinue Pyrukynd if no benefit has been observed by 24 weeks as evaluated by hemoglobin and hemolysis laboratory results and transfusion requirements.

Disease Overview
Pyruvate kinase deficiency is a rare (three to nine cases per one million people), autosomal recessive enzyme defect in red blood cells that is caused by mutations in the pyruvate kinase liver and red blood cell (*PKLR*) gene.[2,3] These alterations result in a deficit of pyruvate kinase activity in red blood

cells which leads to hemolytic anemia of varying severity.[2] Other complications include iron overload (and its sequelae), bilirubin gallstones, pulmonary hypertension, thrombosis, and extramedullary hematopoiesis. Commonly present are compound heterozygous mutations in the gene encoding the L and R isozymes of *PKLR* with more than 300 mutations noted; most patients have at least on missense mutation. More notable management strategies involve blood transfusions, splenectomy, and chelation therapy.

Medical Necessity Criteria

Pyrukynd is considered medically necessary when the following criteria are met:

FDA-Approved Indication

1. **Hemolytic Anemia Due to Pyruvate Kinase Deficiency.** Approve for the duration noted below if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient meets both of the following (a and b):
       - **a)** Presence of at least two variant/mutant alleles in the pyruvate kinase liver and red blood cell (*PKLR*) gene; AND
       - **b)** At least one of the variant/mutant alleles was a missense variant; AND
     - **iii.** Patient meets one of the following (a or b):
       - **a)** Patient has a current hemoglobin level ≤ 10 g/dL; OR
       - **b)** Patient is currently receiving red blood cell transfusions regularly, defined as at least six transfusions within the last year; AND
     - **iv.** The medication is prescribed by or in consultation with a hematologist.
   - **B)** Patient is Currently Receiving Pyrukynd. Approve for 1 year if the patient meets the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient meets both of the following (a and b):
       - **a)** Presence of at least two variant/mutant alleles in the pyruvate kinase liver and red blood cell (*PKLR*) gene; AND
       - **b)** At least one of the variant/mutant alleles was a missense variant; AND
     - **iii.** According to the prescriber, the patient has experienced a benefit from therapy based one of the following (a, b, or c):
       - **a)** Increase in or maintenance of hemoglobin levels; OR
       - **b)** Improvement in or maintenance of hemolysis laboratory parameters; OR
         Note: Examples of laboratory parameters that are markers of hemolysis include indirect bilirubin, lactate dehydrogenase, and haptoglobin.
       - **c)** Decrease in or maintenance of transfusion requirements; AND
     - **iv.** The medication is prescribed by or in consultation with a hematologist.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Patient with Pyruvate Kinase Deficiency Homozygous for the c.1436G>A (p.R479H) Variant/Mutation in the Pyruvate Kinase Liver and Red Blood Cell (*PKLR*) Gene.** Such patients were excluded from the pivotal studies investigating Pyrukynd in patients with pyruvate kinase deficiency because they did not achieve a hemoglobin response in the dose-ranging study.[1]

2. **Patient with Pyruvate Kinase Deficiency with Two Non-Missense Variants/Mutations (without the presence of another missense variant/mutation) in the Pyruvate Kinase Liver and Red Blood Cell (*PKLR*) Gene.** Such patients were excluded from the pivotal studies investigating Pyrukynd because they did not achieve a hemoglobin response in the dose-ranging study.[1]

References

1. Pyrukynd® tablets [prescribing information]. Cambridge, MA: Agios; February 2022.
2. Grace RF, Barcellini W. Management of pyruvate kinase deficiency in children and adults. *Blood*. 2020;136(11):1241-1249.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	**Hemolytic Anemia due to Pyruvate Kinase Deficiency:** For a patient currently receiving therapy, the requirement that the patient has a current hemoglobin level ≤ 12 g/dL was removed.	06/15/2024

The policy effective date is in force until updated or retired.