Drug Coverage Policy

Effective Date.....5/1/2026
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 where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. 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.

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 one missense mutation. More notable management strategies involve blood transfusions, splenectomy, and chelation therapy.

Coverage Policy

POLICY STATEMENT
Prior Authorization is required for benefit coverage of Pyrukynd. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Pyrukynd as well as the monitoring required for adverse events and long-term efficacy, approval requires Pyrukynd to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of Pyrukynd as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information. All documentation must include patient-specific identifying information.

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 ALL of 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 **[documentation required]**; AND
       - **b)** At least one of the variant/mutant alleles was a missense variant **[documentation required]**; 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; OR
   - **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 **[documentation required]**; AND
b) At least one of the variant/mutant alleles was a missense variant **[documentation required]**; 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.

Pyrukynd for any other use is considered not medically necessary including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Alpha-Thalassemia or Beta-Thalassemia.** Aqvesme® (mitapivat tablets) is another mitapivat product that is indicated for the treatment of anemia in adults with alpha-thalassemia or beta-thalassemia.[4] The recommended dosing differs from Pyrukynd.[1,4] Also, Aqvesme is available only through a Risk Evaluation and Mitigation Strategy program because of the risk of hepatocellular injury.[4]

2. **Patient is Currently Receiving Aqvesme.** Aqvesme is another mitapivat product that is indicated for the treatment of anemia in adults with alpha-thalassemia or beta-thalassemia. Concomitant use is not recommended.[4]

3. **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]

4. **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; December 2025.
2. Grace RF, Barcellini W. Management of pyruvate kinase deficiency in children and adults. *Blood*. 2020;136(11):1241-1249.
3. Fattizzo B, Cavallaro F, Marcello APML, et al. Pyruvate kinase deficiency: current challenges and future prospects. *J Blood Med*. 2022;13:461-471.
4. Aqvesme™ tablets [prescribing information]. Cambridge, MA: Agios; December 2025.

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
Annual Revision	No criteria changes.	5/15/2025
Annual Revision	**Added documentation policy statement.** **Added [documentation required]** to "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 for initial therapy and patients currently receiving therapy." **Conditions Not Covered:** The condition of Alpha-Thalassemia or Beta-Thalassemia was added. Also, an exclusion was added regarding a patient who is currently receiving Aqvesme.	5/1/2026

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