PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Pyrukynd Prior Authorization Policy
- Pyrukynd® (mitapivat tablets – Agios)

REVIEW DATE: 03/22/2023

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. 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 NATIONAL FORMULARY COVERAGE:

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 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 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.

POLICY STATEMENT

Prior Authorization is recommended for prescription 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, Pyrukynd 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.

Pyrukynd® (mitapivat tablets (Agios)
is(are) covered as medically necessary when the following criteria is(are) met for fda-approved indication(s) or other uses with supportive evidence (if applicable):

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 criteria (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 **[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.** 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, iv, and v):
     - **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 has a current hemoglobin level ≤ 12.0 g/dL; AND
     - **iv.** 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; OR

v. Medication is prescribed by or in consultation with a hematologist.

CONDITIONS NOT COVERED

Pyrukynd® (mitapivat tablets (Agios)
is(are) considered experimental, investigational or unproven for ANY other use(s) 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.
3. Fattizzo B, Cavallaro F, Marcello APML, et al. Pyruvate kinase deficiency: current challenges and future prospects. *J Blood Med*. 2022;13:461-471.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	03/02/2022
Selected Revision	**Hemolytic Anemia due to Pyruvate Kinase Deficiency:** For a patient currently receiving therapy, the requirement that the patient have a current hemoglobin level ≤ 13 g/dL was changed to ≤ 12 g/dL. Also, for this population, the requirement that the patient has experienced a benefit from therapy was changed from requiring that the patient meet "all" of the following to "one" of the following: increase in or maintenance of hemoglobin levels; improvement in or	03/09/2022

	maintenance of hemolysis laboratory parameters; or decrease in or maintenance of transfusion requirements.	
Annual Revision	No criteria changes.	03/22/2023