

CLINICAL POLICY

Mitapivat



Clinical Policy: Mitapivat (Pyrukynd)

Reference Number: CP.PHAR.558

Effective Date: 10/2022

Last Review Date: 11/2025

Description

Mitapivat (Pyrukynd[®]) is a pyruvate kinase (PK) activator.

FDA Approved Indication(s)

Pyrukynd is indicated for the treatment of hemolytic anemia in adults with PK deficiency.

Policy/Criteria

It is the policy of PA Health & Wellness[®] that Pyrukynd is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Pyruvate Kinase Deficiency (must meet all):

1. Diagnosis of PK deficiency confirmed by *PLKR* gene molecular analysis and one of the following (a or b):
 - a. Both of the following (i and ii):
 - i. Presence of at least 2 mutant alleles in the PKLR gene;
 - ii. At least 1 mutant allele is a missense mutation;
 - b. Hemolytic anemia with laboratory evidence of reduced red blood cell PK enzymatic activity;
2. Prescribed by or in consultation with a hematologist;
3. Age \geq 18 years;
4. Member is not homozygous for the R479H mutation or have 2 non-missense mutations (without the presence of another missense mutation) in the PKLR gene;
5. If member received \leq 4 blood transfusions in the last 12 months, recent (within the last 30 days) hemoglobin concentration \leq 10 g/dL;
6. Prescribed concurrently with oral folic acid;
7. Dose does not exceed both of the following (a and b):
 - a. 100 mg per day;
 - b. 2 tablets per day.

Approval duration: 6 months

B. Other diagnoses/indications

1. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53.

II. Continued Therapy

A. Pyruvate Kinase Deficiency (must meet all):

1. Currently receiving medication via PA Health and Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care Policy (PA.PHARM.01) applies;

2. Member is responding positively to therapy as evidenced by, including but not limited to, improvement in any of the following parameters from baseline prior to Pyrukynd initiation:
 - a. Reduced transfusion burden;
 - b. Increase in hemoglobin of at least 1.5 g/dL;
3. If request is for a dose increase, new dose does not exceed both of the following (a and b):
 - a. 100 mg per day;
 - b. 2 tablets per day.

Approval duration: 12 months

B. Other diagnoses/indications

1. Currently receiving medication via PA Health & Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care Policy (PA.PHAR.01) applies.
Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

III. Diagnoses/Indications for which coverage is NOT authorized:

- A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policy – PA.CP.PMN.53 or evidence of coverage documents

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration

PK: pyruvate kinase

PKLR: pyruvate kinase liver and red blood cell

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

None reported

Appendix D: General Information

- Patients who were homozygous for the c.1436G>A (p.R479H) variant or had 2 non-missense variants (without the presence of another missense variant) in the PKLR gene were excluded in the clinical trial because these patients did not achieve hemoglobin response (change from baseline in Hb \geq 1.5 g/dL at > 50% assessments) in the dose-ranging study.
- The 2024 International expert guidelines for PK deficiency recommend diagnostic confirmation with gene molecular analysis of the *PLKR* gene. If there aren't two known pathogenic mutations in *PLKR* identified, then the panel recommends confirmation of a diagnosis of PK deficiency with PK enzyme activity measurement. This is because

confirmatory reduced PK enzyme activity should be obtained where possible to confirm pathogenicity of novel *PKLR* variants or variants of unknown significance detected by molecular testing.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
PK deficiency	Initial: 5 mg PO BID Dose may be increased every 4 weeks based on response and tolerance to 20 mg BID up to a maximum of 50 mg BID	100 mg/day

VI. Product Availability

Oral tablets: 5 mg, 20 mg, 50 mg

VII. References

1. Pyrukynd Prescribing Information. Cambridge, MA: Agios Pharmaceuticals, Inc.; January 2025. Available at <https://www.agios.com/prescribinginfo.pdf>. Accessed July 15, 2025.
2. Al-Samkari H, Galactéros F, Glenthøj A, et al. Mitapivat versus placebo for pyruvate kinase deficiency. *N Engl J Med*. 2022;386(15):1432-1442.
3. Glenthøj A, van Beers EJ, Al-Samkari H, et al. Mitapivat in adult patients with pyruvate kinase deficiency receiving regular transfusions (ACTIVATE-T): a multicentre, open-label, single-arm, phase 3 trial. *Lancet Haematol*. 2022;9(10):e724-e732. doi:10.1016/S2352-3026(22)00214-9 Grace RF, Barcellini W. Management of pyruvate kinase deficiency in children and adults. *Blood*: September 10, 2020; 136 (11): 1241-1249.
4. Al-Samkari H, Shehata N, Lang-Robertson K, et al. Diagnosis and management of pyruvate kinase deficiency: international expert guidelines. *Lancet Haematol*. 2024;11(3):e228-e239.

Reviews, Revisions, and Approvals	Date
Policy created	10/2022
4Q 2023 annual review: no significant changes; references reviewed and updated.	10/2023
4Q 2024 annual review: clarified requirement for <i>PKLR</i> gene molecular analysis for diagnosis of PK deficiency to align with 2024 international expert guidelines; clarified that homozygosity for the R479H mutation and presence of 2 non-missense mutations is specific to the <i>PKLR</i> gene; references reviewed and updated.	10/2024
4Q 2025 annual review: no significant changes; for continued therapy, clarified that reduced transfusion burden also applies to difference from baseline prior to Pyrukynd initiation; references reviewed and updated.	10/2025