Clinical Policy: Mitapivat (Pyrukynd)

Reference Number: CP.PHAR.558
Effective Date: 10/2022
Last Review Date: 11/2023

Description
Mitapivat (Pyrukynd®) is an 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 one of the following (a or b):
   a. Presence of at least 2 mutant alleles in the PKLR gene, of which at least 1 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 ≥ 18 years;
4. Member is not homozygous for the R479H mutation or have 2 non-missense mutations (without the presence of another missense mutation);
5. If member received no more than 4 blood transfusions in the last 12 months, recent (within the last 30 days) hemoglobin concentration ≤ 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.LTSS.PHAR.01) applies;
2. Member is responding positively to therapy as evidenced by, including but not limited to, improvement in any of the following parameters:

a. Reduced transfusion burden;
b. Increase in hemoglobin of at least 1.5 g/dL from baseline prior to Pyrukynd initiation;

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.LTSS.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 ≥ 1.5 g/dL at > 50% assessments) in the dose-ranging study.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
PK deficiency	Initial: 5 mg PO BID	100 mg/day

Indication	Dosing Regimen	Maximum Dose
	Dose may be increased every 4 weeks based on response and tolerance to 20 mg BID up to a maximum of 50 mg BID	

VI. Product Availability

Oral tablets: 5 mg, 20 mg, 50 mg

VII. References

1. Pyrukynd Prescribing Information. Cambridge, MA: Agios Pharmaceuticals, Inc.; February 2022. Available at https://www.agios.com/prescribinginfo.pdf. Accessed July 10, 2023.
2. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). NCT03548220: A Study to Evaluate Efficacy and Safety of AG-348 in Not Regularly Transfused Adult Participants With Pyruvate Kinase Deficiency (PKD). Updated November 10, 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT03548220?term=NCT03548220. Accessed September 9, 2021.
3. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). NCT03559699: A Study Evaluating the Efficacy and Safety of AG-348 in Regularly Transfused Adult Participants With Pyruvate Kinase Deficiency (PKD). Updated December 8, 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT03559699?term=NCT03559699&draw=2&rank=1. Accessed September 9, 2021.
4. Al-Samkari H, Galacteros F, Glenthoj A, et al. ACTIVATE: A Phase 3, randomized, multicenter, double-blind, placebo-controlled study of mitapivat in adults with pyruvate kinase deficiency who are not regularly transfused. European Hematology Association Virtual Congress 2021: Abstract S270. Available at: https://library.ehaweb.org/eha/2021/eha2021-virtual-congress/324678. Accessed September 9, 2021.
5. Glenthoj A, van Beers EJ, Al-Samkari H, et al. ACTIVATE-T: A phase 3, open-label, multicenter study of mitapivat in adults with pyruvate kinase deficiency who are regularly transfused. European Hematology Association Virtual Congress 2021: Abstract S271. Available at: https://library.ehaweb.org/eha/2021/eha2021-virtual-congress/324679. Accessed September 9, 2021.
6. Grace RF, Barcellini W. Management of pyruvate kinase deficiency in children and adults. Blood: September 10, 2020; 136 (11): 1241-1249.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	10/2022	
4Q 2023 annual review: no significant changes; references reviewed and updated.	10/2023	