Clinical Policy: Mitapivat (Pyrukynd)

Reference Number: ERX.SPA.456
Effective Date: 02.17.22
Last Review Date: 11.22
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

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
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ 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 100 mg per day.

Approval duration: 6 months

B. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Pyruvate Kinase Deficiency (must meet all)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
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 100 mg per day.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 – ERX.PA.01 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 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.; February 2022. Available at https://www.agios.com/prescribinginfo.pdf. Accessed August 1, 2022.
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 pre-emptively	09.28.21	11.21
RT4: Converted PEPP to post-FDA-approved status. No significant changes	03.08.22	
4Q 2022 annual review: no significant changes; references reviewed and updated.	08.01.22	11.22

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.