Clinical Policy: Mitapivat (Pyrukynd , Aqvesme)

Reference Number: CP.PHAR.558
Effective Date: 10/2022
Last Review Date: 01/2026

Description
Mitapivat (Pyrukynd® , Aqvesme™) is a pyruvate kinase (PK) activator.

FDA Approved Indication(s)
Pyrukynd is indicated for the treatment of hemolytic anemia in adults with PK deficiency.

Aqvesme is indicated for the treatment of anemia in adults with alpha- or beta-thalassemia.

Policy/Criteria
It is the policy of PA Health & Wellness® that Pyrukynd and Aqvesme are **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. Request is for Pyrukynd;
3. Prescribed by or in consultation with a hematologist;
4. Age ≥ 18 years;
5. 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;
6. If member received ≤4 blood transfusions in the last 12 months, recent (within the last 30 days) hemoglobin concentration ≤ 10 g/dL;
7. Prescribed concurrently with oral folic acid;
8. Pyrykynd is not prescribed concurrently with Aqvesme;
9. 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. Thalassemia (must meet all)**:**

1. Diagnosis of thalassemia with one of the following genotypes (a, b, or c):
   a. Beta thalassemia;
   b. Hemoglobin E/beta thalassemia;
   c. Hemoglobin H/alpha thalassemia;
2. Request is for Aqvesme;

3. Prescribed by or in consultation with a hematologist;
4. Age ≥ 18 years;
5. Member meets one of the following (a or b):
   a. Member has received ≥ 6 red blood cell (RBC) units in the last 6 months;
   b. Recent (within the last 30 days) hemoglobin concentration ≤ 10 g/dL;
6. Aqvesme is not prescribed concurrently with Pyrykynd or Reblozyl®;
7. Dose does not exceed both of the following (a and b):
   a. 200 mg per day;
   b. 2 tablets per day.

Approval duration: 12 months

C. 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. Request is for Pyrukynd;
3. 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;
4. Pyrykynd is not prescribed concurrently with Aqvesme;
5. 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. Thalassemia (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. Request is for Aqvesme;
3. 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 Aqvesme initiation:
   a. Reduced transfusion burden;
   b. Increase in hemoglobin of at least 1 g/dL;
4. Aqvesme is not prescribed concurrently with Pyrykynd or Reblozyl;
5. If request is for a dose increase, new dose does not exceed both of the following (a and b):

a. 200 mg per day;
b. 2 tablets per day.

Approval duration: 12 months

C. 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
RBC: red blood cell

Appendix B: Therapeutic Alternatives
Not applicable

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): none reported
- Boxed warning(s): hepatocellular injury (*Aqvesme only*)

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.
- 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
Mitapivat (Pyrukynd)	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
Mitapivat (Aqvesme)	Alpha- and beta-thalassemia	100 mg PO BID	200 mg/day

VI. Product Availability

Drug Name	Availability
Mitapivat (Pyrukynd)	Oral tablets: 5 mg, 20 mg, 50 mg
Mitapivat (Aqvesme)	Oral tablet: 100 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. Aqvesme Prescribing Information. Cambridge, MA: Agios Pharmaceuticals, Inc.; December 2025. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/216196s003lbl.pdf. Accessed December 30, 2025.

PK deficiency

3. 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.
4. 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.
5. Grace RF, Barcellini W. Management of pyruvate kinase deficiency in children and adults. Blood: September 10, 2020; 136 (11): 1241-1249.
6. 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.

Thalassemia

7. Taher AT, Farmakis D, Porter JB, et al. Guidelines for the management of transfusion dependent thalassemia (TDT) 5th Edition. Thalassemia International Federation (2025). Available at: https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-themanagement-of-transfusion-dependent-β-thalassaemia-5th-edition-2025/. Accessed December 30, 2025.
8. Taher A, Musallam K, Cappellini MD. Guidelines for the management of non-transfusion dependent β-thalassaemia 3rd edition. Thalassaemia International Federation. 2023. Available at: https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-managementof-non-transfusion-dependent-%ce%b2-thalassaemia-3rd-edition-2023/. Accessed December 30, 2025.

9. Amid A, Lal A, Coates TD, Fucharoen S, et al. Guidelines for the management of αthalassaemia. Thalassaemia International Federation. 2023. Available at: https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-%ce%b1-thalassaemia/?-thalassaemia%2F. Accessed December 30, 2025.

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 *PLKR* 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 *PKLR* 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
RT4: added Aqvesme for treatment of anemia in adults with thalassemia to policy.	01/2026