Clinical Policy: Mitapivat (Pyrukynd, Aqvesme)

Reference Number: CP.PHAR.558
Effective Date: 02.17.22
Last Review Date: 05.26
Line of Business: Commercial, HIM, Medicaid

Revision Log

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

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

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

It is the policy of health plans affiliated with Centene Corporation® 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. Both of the following (i and ii):
      i. Member has received ≥ 6 red blood cell (RBC) units in the last 6 months;
      ii. If request is for beta thalassemia or Hemoglobin E/beta thalassemia, failure of Reblozyl®*, unless contraindicated or clinically significant adverse effects are experienced^;
      ^For Illinois HIM requests, the step therapy requirements above do not apply as of 1/1/2026 per IL HB 5395
      **Prior authorization may be required for Reblozyl*
   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 (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Pyruvate Kinase Deficiency (must meet all)**:**
1. Member meets one of the following (a or b):

a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*

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. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
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 (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or

b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid 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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Thalassemia		
Reblozyl® (luspatercept-aamt)	1 mg/kg SC every 3 weeks	1.25 mg/kg/3 weeks

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

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

Drug Name	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	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. Template changes applied to other diagnoses/indications and continued therapy section.	08.01.22	11.22
4Q 2023 annual review: no significant changes; references reviewed and updated.	07.10.23	11.23
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.	07.19.24	11.24
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.	07.15.25	11.25
RT4: added Aqvesme for treatment of anemia in adults with thalassemia to policy.	12.30.25	
Per March SDC: for beta thalassemia and Hemoglobin E/beta thalassemia, added redirection to Reblozyl for members that received ≥ 6 RBC units in the last 6 months.	03.10.26	05.26

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health

plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

©2021 Centene Corporation. All rights reserved. All materials are exclusively owned by Centene Corporation and are protected by United States copyright law and international copyright law. No part of this publication may be reproduced, copied, modified, distributed, displayed, stored in a retrieval system, transmitted in any form or by any means, or otherwise

published without the prior written permission of Centene Corporation. You may not alter or remove any trademark, copyright or other notice contained herein. Centene® and Centene Corporation® are registered trademarks exclusively owned by Centene Corporation.