**Original Effective Date: 04/28/2022**
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**Last P&T Approval/Version: 01/29/2025**
**Next Review Due By: 01/2026**
**Policy Number: C22822-A**

# Pyrukynd (mitapivat)

## PRODUCTS AFFECTED

Pyrukynd (mitapivat)

## COVERAGE POLICY

*Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.*

***Documentation Requirements:***
*Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.*

**DIAGNOSIS:**
Pyruvate kinase (PK) deficiency

**REQUIRED MEDICAL INFORMATION:**
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. PYRUVATE KINASE (PK) DEFICIENCY
1. Documented diagnosis of pyruvate kinase deficiency
   AND

2. Documentation diagnosis confirmed with genetic testing showing:
    a. Member has at least two mutant alleles in the PKLR (pyruvate kinase liver and red blood cell) gene, of which at least one is a missense mutation
    AND
    b. Member is not homozygous for the R479H mutation
    AND
    c. Member does not have two non-missense variants in the PKLR gene, without the presence of another missense variant

AND

3. Documentation that in the previous 12 months, member has required at least 6 red blood cell transfusions
AND
4. Documentation that member's baseline hemoglobin is ≤ 10 mg/dL [DOCUMENTATION REQUIRED]
AND
5. Prescriber attests a recent review of member's current medication has been completed and prescriber has not found any interactions or will appropriately monitor for adverse reactions and hemoglobin due to the interactions.
NOTE: Avoid use of Pyrukynd concomitantly with strong CYP3A inhibitors or inducers. When used with a moderate CYP3A inhibitor, Pyrukynd dose should not exceed 20 mg twice daily.
AND
6. Prescriber attests that member will receive folic acid supplementation throughout treatment with requested therapy
AND
7. Prescriber attests that member does not have moderate or severe hepatic dysfunction

**CONTINUATION OF THERAPY:**

A. PYRUVATE KINASE (PK) DEFICIENCY:

1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
AND
2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
AND
3. Documentation of positive clinical response as demonstrated by an increase in hemoglobin ≥ 1.5 mg/dL from baseline and/or documented reduction in transfusion burden [DOCUMENTATION REQUIRED]
AND
4. Prescriber attests a recent review of member's current medication has been completed and prescriber has not found any interactions or will appropriately monitor for adverse reactions and hemoglobin due to the interactions.
NOTE: Avoid use of Pyrukynd concomitantly with strong CYP3A inhibitors or inducers. When used with a moderate CYP3A inhibitor, Pyrukynd dose should not exceed 20 mg twice daily.

**DURATION OF APPROVAL:**

Initial authorization: 6 months, Continuation of Therapy: 12 months

**PRESCRIBER REQUIREMENTS:**

Prescribed by or in consultation with a board-certified hematologist. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests.]

**AGE RESTRICTIONS:**
18 years of age and older

**QUANTITY:**
One (1) 28-day pack per month
One Taper Pack, as needed for interruption in treatment or discontinuation

**Maximum Quantity Limits –** 50 mg twice daily
If Pyrukynd is used with a moderate CYP3A inducer (e.g., efavirenz) and therapy with the inducer has no alternative - 100 mg twice daily

**PLACE OF ADMINISTRATION:**
The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

## DRUG INFORMATION

**ROUTE OF ADMINISTRATION:**
Oral

**DRUG CLASS:**
Pyruvate Kinase Activators

**FDA-APPROVED USES:**
Indicated for the treatment of hemolytic anemia in adults with pyruvate kinase (PK) deficiency

**COMPENDIAL APPROVED OFF-LABELED USES:**
None

## APPENDIX

**Dose Titration Schedule for initiation of treatment with Pyrukynd:**

| Duration | Dosage |
|---|---|
| Week 1 through Week 4 | 5 mg twice daily |
| Week 5 through Week 8 | If Hb is below normal range or patient has required a transfusion within the last 8 weeks:<br>• Increase to 20 mg twice daily and maintain for 4 weeks.<br>If Hb is within normal range and patient has not required a transfusion within the last 8 weeks:<br>• Maintain 5 mg twice daily. |
| Week 9 through Week 12 | If Hb is below normal range or patient has required a transfusion within the last 8 weeks:<br>• Increase to 50 mg twice daily and maintain thereafter.<br>If Hb is within normal range and patient has not required a transfusion within the last 8 weeks:<br>• Maintain current dose (5 mg twice daily or 20 mg twice daily). |
| Maintenance | If Hb decreases, consider up-titration to the maximum of 50 mg twice daily as per the above schedule. |

## BACKGROUND AND OTHER CONSIDERATIONS

**BACKGROUND:**
Pyruvate kinase (PK) deficiency is a rare hereditary disorder which affects red blood cell (RBC) glycolysis. Pyruvate kinase catalyzes the final step in glycolysis, which is needed to produce adenosine triphosphate (ATP) in the red blood cell. Without ATP, the RBCs breakdown prematurely. Alterations in the PKLR gene are inherited in an autosomal recessive manner and result in a deficiency in the pyruvate kinase enzyme. Due to this deficiency RBCs last days to weeks, rather than the typical average of 120 days. This results in a lifelong, chronic hemolytic anemia. The estimated disease prevalence is 1 per 20,000 in the Caucasian population. There is a higher prevalence in the Pennsylvania Amish community due to the founder effect.

The signs and symptoms of pyruvate kinase deficiency can include anemia, fatigue, exercise intolerance, jaundice, memory loss, and difficulty concentrating. Additional complications are also observed in individuals with PK deficiency, including iron overload, gallstones, bone fracture/osteoporosis, and spleen enlargement. Management of PK deficiency is supportive and includes RBC transfusions, splenectomy, cholecystectomy, and iron chelation therapy.

Pyrukynd (mitapivat) is an oral small molecule allosteric activator of the pyruvate kinase enzyme. Mitapivat binds to and activate the PK enzyme, increasing ATP production in the RBC. Mitapivat was studied in two clinical trials: ACTIVATE (NCT03548220) and ACTIVATE-T (NCT03559699). ACTIVATE was a phase 3, randomized, double-blind placebo-controlled trial in 80 patients with pyruvate kinase deficiency (PKD), who were not regularly receiving blood transfusion. The study was divided into two segments. The first was a dose optimization period in which the dose was started at 5 mg twice daily followed by sequential dose increases to 20 mg twice daily and 50 mg twice daily, depending upon tolerance. The second part was a fixed dose period, in which the participants received their optimized dose. Participants were 18 years and older, with a confirmed diagnosis of PKD documented by the presence of at least 2 mutant alleles in the PKLR gene, of which at least 1 is a missense mutation. Participants were excluded if they were homozygous for the R479H mutation or have 2 non-missense mutations, without the presence of another missense mutation, in the PKLR gene. Baseline hemoglobin concentration for all participants was requires to be less than or equal to 10.0 g/dL regardless of gender. Participants could have received no more than 4 transfusions in the 12 months prior to the study and no transfusion sin the 3 months prior to the study. Hemoglobin response was defined as a ≥1.5 g/dL increase in Hb from baseline sustained at two or more scheduled assessments (Weeks 16, 20, and 24) during the fixed-dose period without transfusions. Hemoglobin response was achieved in 16 participants (40%, n=40) in the Pyrukynd group and 0 participants in the placebo group (n=40), which was a statistically significant difference (p<0.0001). ACTIVATE-T evaluated the efficacy of mitapivant in participants that received regular transfusions. This trial was a multinational single arm trial in 27 adults with PKD. Participants were required to have received a minimum of 6 transfusion episodes in the 52- week period prior to study consent. Participants were required to have a confirmed diagnosis of PKD documented by the presence of at least 2 mutant alleles in the PKLR gene, of which at least 1 is a missense mutation. Participants were excluded if they were homozygous for the R479H mutation or have 2 non-missense mutations, without the presence of another missense mutation, in the PKLR gene. Participants (n=27) had a median of 9 transfusion episodes prior to the study, with a median of 7 RBC units transfused standardized to 24 weeks. Efficacy was defined as a ≥ 33% reduction in RBC units transfused during the study period compared to the participants baseline. Nine participants (33%) achieved the defined transfusion response (95% CI 17,54) and six participants (22%) were transfusion free (95% CI 9, 42).

In the ACTIVATE trial, the most In the ACTIVATE trial, the most common adverse reactions including laboratory abnormalities (≥ 10%) in patients with PK deficiency were estrone decreased (males), increased urate, back pain, estradiol decreased (males), and arthralgia. The adverse reactions reported in the population of patients who were regularly transfused (ACTIVATE-T) were consistent with that seen in ACTIVATE.

**CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:**
All other uses of Pyrukynd (mitapivat) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Pyrukynd (mitapivat) include: avoid concomitant use with strong CYP3A inhibitors and inducers, avoid concomitant use with sensitive CYP3A, CYP2B6, CYP2C substrates including hormonal contraceptives, that have a narrow therapeutic index, avoid use in patients with moderate or severe hepatic impairment.

**OTHER SPECIAL CONSIDERATIONS:**
Pyrukynd (mitapivat) is taken with or without food and is swallowed whole. Tablets are not to be split, crushed, chewed, or dissolved. Blister wallets should be stored in the original carton until use.

Pyrukynd (mitapivat) should be started at 5 mg twice daily for the first 4 weeks. The dose may then be increased to 20 mg twice daily for the next 4 weeks (weeks 5 through 8), if the member's hemoglobin is below normal or the member has required a transfusion within the last 8 weeks.
The dose may be increased to 50 mg twice daily (maximum dose), if the member's hemoglobin is below normal or the member has required a transfusion within the last 8 weeks. If the member achieves a hemoglobin above more and has not required a transfusion in the previous 8 weeks, the current dose (5 mg, 20 mg or 50 mg twice daily) should be maintained.

To avoid the risk of acute hemolysis, Pyrukynd (mitapivat) should not be abruptly interrupted or discontinued. The dose should be tapered over 7 to 14 days, dependent upon the current dose.

Dose Taper Schedule:

| Current Dose | Day 1-7 | Day 8-14 | Day 15 |
|---|---|---|---|
| 5 mg twice daily | 5 mg once daily | Discontinue | |
| 20 mg twice daily | 20 mg once daily | 5 mg once daily | Discontinue |
| 50 mg twice daily | 50 mg once daily | 20 mg once daily | Discontinue |

Special Populations:
Safety and efficacy of Pyrukynd (mitapivat) has not been established in pediatric patients. Mitapivat undergoes extensive hepatic metabolism. Moderate and severe hepatic impairment is expected to increase the systemic exposure, therefore use should be avoided in this population.

## CODING/BILLING INFORMATION

***CODING DISCLAIMER.*** *Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.*

| HCPCS CODE | DESCRIPTION |
|---|---|
| NA | |

**AVAILABLE DOSAGE FORMS**:
Pyrukynd TABS 5MG
Pyrukynd TABS 20MG
Pyrukynd TABS 50MG
Pyrukynd Taper Pack TBPK 5MG
Pyrukynd Taper Pack TBPK 7 x 20 MG &7 x 5 MG
Pyrukynd Taper Pack TBPK 7 x 50 MG &7 x 20 MG

## REFERENCES


1. Pyrukynd (mitapivat) tablet [prescribing information], Cambridge, MA: Agios Pharmaceuticals, Inc., January 2025.
2. Boscoe, A. N., Yan, Y., Hedgeman, E., van Beers, E. J., Al-Samkari, H., Barcellini, W., Eber, S. W., Glader, B., Yaish, H. M., Chonat, S., Sharma, M., Kuo, K., Neufeld, E. J., Wang, H., Verhovsek, M., Sheth, S., & Grace, R. F. (2021). Comorbidities and complications in adults with pyruvate kinase deficiency. *European journal of haematology*, *106*(4), 484–492. https://doi.org/10.1111/ejh.13572
3. Boscoe AN, et al. Comorbidities and complications in adults with pyruvate kinase deficiency. Eur J Haematol. 2021;106(4):484-492. doi:10.1111/ejh.13572
4. Pyruvate Kinase Deficiency - NORD (National Organization for Rare Disorders). (2022). Retrieved 28 March 2022, from https://rarediseases.org/rare-diseases/pyruvate-kinase- deficiency/


| SUMMARY OF REVIEW/REVISIONS | DATE |
|---|---|
| REVISION- Notable revisions:<br>Continuation of Therapy<br>References | Q1 2025 |
| REVISION- Notable revisions:<br>Required Medical Information<br>Continuation of Therapy<br>Quantity | Q1 2024 |
| REVISION- Notable revisions:<br>Required Medical Information<br>Continuation of Therapy<br>Contraindications/Exclusions/Discontinuation | Q1 2023 |
| INITIAL REVIEW COMPLETED | Q2 2022 |