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Medication Policy Manual | **Policy No:** dru719

Topic: Pyrukynd, mitapivat | **Date of Origin:** September 1, 2022

Committee Approval Date: June 5, 2025 | **Next Review Date:** 2026

Effective Date: August 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Pyrukynd (mitapivat) is an oral medication used to treat a specific blood disorder [hemolytic anemia in adult patients with pyruvate kinase deficiency (PKD)].

Policy/Criteria

Most contracts require pre-authorization approval of Pyrukynd (mitapivat) prior to coverage.

I. Continuation of therapy (COT): Pyrukynd (mitapivat) may be considered medically necessary for COT when criterion A or B below is met.

A. For diagnoses NOT listed in the coverage criteria below, full criteria below must be met.

OR

B. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Pyrukynd (mitapivat) may be considered medically necessary when there is clinical documentation (including but not limited to chart notes) that criteria A through C below are met.

A. A diagnosis of **pyruvate kinase deficiency** (PKD), established by a hematologist.

AND

B. Genetic confirmation of PKD AND documentation of both of the following (1 and 2):

1. Presence of at least two variant alleles in the PKLR (pyruvate kinase liver and red blood cell) gene, one of which must be a missense variant.

AND

2. Negative for homozygous variant R479H in the PKLR gene.

AND

C. Transfusion-dependent, with one or both of the following (1 or 2):

1. Transfusion dependance, defined as use of at least six red blood cell transfusions (RBCT) in the past 12 months.

OR

2. Red blood cell transfusion therapy (RBCT) or iron chelation therapy (ICT) has been ineffective, not tolerated, or use is contraindicated (as defined in *Appendix 1*).

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Pyrukynd (mitapivat) coverable only under the pharmacy benefit (as a self-administered medication).

B. When pre-authorization is approved, Pyrukynd (mitapivat) will be authorized in quantities of up to one-pack (56 tablets) per 28 days allowing for upward dose titration (see *Appendix 2)* for an initial period of 24 weeks.

PLEASE NOTE: In the case of discontinuation of Pyrukynd (mitapivat), one-time dose taper pack will be authorized to allow for a slow tapered discontinuation (as defined in *Appendix* 3).

C. Initial and Continued Authorization:

1. Authorization **shall** be reviewed every 24 weeks.

2. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met and Pyrukynd (mitapivat) is providing benefit, including but not limited to disease symptom improvement (such as improvement in activities of daily living, exercise tolerance, shortness of breath, or jaundice) and/or providing a positive hematologic response (increase in hemoglobin [Hb] of ≥1.5 g/dl or a reduction in red blood cell transfusions from baseline).

IV. Pyrukynd (mitapivat) is considered investigational when used for all other conditions including but not limited to:

A. Sickle cell disease (SCD).

B. Alpha thalassemia.

C. Beta thalassemia.

Position Statement

Summary

- Pyrukynd (mitapivat) is an orally administered medication that activates pyruvate kinase and is indicated to treat hemolytic anemia in patients with PKD.
- The intent of the policy is to limit coverage of Pyrukynd (mitapivat) where it has been studied and shown to be safe effective (as outlined in the coverage criteria), up to the doses shown to be safe and effective in trials, including:
  - Patients with transfusion-dependent PKD despite standard transfusion therapy.
- Pyrukynd (mitapivat) was approved by the FDA based on two small placebo-controlled phase 3 trials, which reported significant increases in Hb in non-transfusion dependent PKD and a reduction in transfusion burden with transfusion-dependent PKD with use of Pyrukynd (mitapivat). Improvement in Hb and/or reduction in transfusion burden are unvalidated surrogate markers. The effect on clinically relevant outcomes, such as quality of life and prevention of PKD-associated complications, is unknown at this time.
- Pyrukynd (mitapivat) is FDA-approved to treat PKD hemolytic anemia regardless of transfusion status. There is a lack of known benefit of Pyrukynd (mitapivat) for non-transfusion dependent PKD (< 6 RBCTs in past 12 months) over current standard therapy.
- Standard of care supportive therapies for PKD, including RBCTs with ICT, have proven clinical outcomes including reduction of morbidity. However, not all patients tolerate or respond adequately to standard therapy. Therefore, Pyrukynd (mitapivat) is a coverable

treatment option when standard of care therapies are ineffective, not tolerated, or use is contraindicated.

- There are no clinical trials that compared the safety and efficacy of Pyrukynd (mitapivat) to any other treatment options, including RBCTs with ICT.
- Pyrukynd (mitapivat) is coverable for the doses shown to be safe and effective in clinical trials. Doses above this have not been shown to be safe and effective.
- Trials are ongoing in a variety of diagnoses. However, the use of Pyrukynd (mitapivat) in clinical settings other than described in the coverage criteria are considered investigational.

PDK Background [1-4]

- PKD is a rare, life-long, inherited disorder caused by variants in the PKLR gene resulting in the premature destruction of RBC's, leading to hemolytic anemia. The anemia is associated with morbidity from frequent RBCTs and resulting iron overload, as well as long term osteoporosis, thrombosis, and decreased overall quality of life.
- PKD can be diagnosed at any age but typically is diagnosed early in life due to patients requiring RBCTs to alleviate the symptoms of anemia such as fatigue, shortness of breath, bone pain, splenomegaly, gallstones, and jaundice. PKD is likely underdiagnosed due to the rarity of disease, and absence or variability of symptoms even in the presence of low Hb.
- Diagnosis of PKD includes presence of hemolysis, PK enzyme levels in blood, and confirmatory PKLR gene testing.
- An international guideline recommends that adults with PK deficiency who receive regular transfusions and have not undergone splenectomy receive a trial of mitapivat therapy before consideration of splenectomy (low certainty of evidence, strong recommendation, 100% agreement). Splenectomy is permanent and comes with potential irreversible harms and heightened lifelong risks. Mitapivat can be easily discontinued and has shown a favorable safety profile in clinical trials.[5] Historically, PKD is managed with supportive therapy, such as RBCTs, ICT, folic acid supplementation, and splenectomy. Treatment is tailored to each patient's disease manifestations and lifestyle needs.
    * RBCTs are the mainstay supportive therapy, along with ICT for associated iron overload.
    * Splenectomy is an option for patients requiring frequent transfusions. Though not curative, splenectomy is proven to reduce transfusions and improve symptoms. Risks include infections and thrombosis.
    * Hematopoietic stem cell transplant (HSCT) is potentially curative for PKD. However, the use is not well defined, nor is HSCT widely used due to associated risks of morbidity and mortality.
- Treatment of PKD is based on symptoms, along with hemolysis markers. However, most patients will require transfusions at some point regardless of their baseline symptoms, with acute stressors which increase hemolysis, such as infection and pregnancy.

Clinical Efficacy [4 6 7]

- The safety and efficacy of Pyrukynd (mitapivat)was evaluated in two phase 3 trials (ACTIVATE and ACTIVATE-T) in adults with PKD.
    * All patients in both studies had genetically confirmed PKD (defined as possessing two variant alleles in the PKLR gene, of which at least one was missense variant).
    * All patients were negative for homozygous R479H variant. In Phase 2 trials, patients who were homozygous for either non missense variants or positive for R479H variants had no response to Pyrukynd (mitapivat) and were excluded from Phase 3 trials.
    * Over 70% of patients in these trials had a previous splenectomy.
    * ACTIVATE (n=80) was a double-blind, placebo controlled, randomized trial in adults with non-transfusion dependent PKD (defined as ≤ 4 RBCTs in previous year) with a baseline Hb of ≤ 10g/dl.
        - All patients were considered non-transfusion dependent. More than 90% of enrolled patients had ≤ 1 RBCT in the prior year.
        - Pyrukynd (mitapivat) dose was titrated based on Hb or transfusion response over 12 weeks, then administered as a fixed dose for 12 weeks.
        - The primary endpoint was the percent achieving a ≥ 1.5 g/dl increase in Hb from baseline.
        - Significantly more patients (40%) met the hemoglobin improvement endpoint as compared to placebo (0%).
        - QOL assessments were a secondary endpoint. However, the QOL assessment used is unvalidated, and the reported improvement versus placebo was minimal.
        - Given the absence of proven meaningful health outcome, the use of Pyrukynd (mitapivat) in non-transfusion dependent PKD is considered not medically necessary and not coverable.
    * ACTIVATE-T (n=27) was a single-arm, open-label trial in adults with transfusion-dependent PKD (defined as ≥ 6 RBCTs in the previous year).
        - The primary endpoint was the percent of patients achieving ≥ 33% reduction in RBC units transfused compared to historical burden (patients served as their own control).
        - Pyrukynd (mitapivat) dose was titrated based on Hb or transfusion response over 16 weeks, then administered as a fixed dose for 24 weeks.
        - 33%patients (n=9) met the transfusion-reduction endpoint when compared to their historical burden. Of the responders, 6 patients became transfusion-free during the fixed-dose period.
- Increasing Hb as well as reducing transfusions are surrogate markers and have not been established to accurately predict improvement in clinically relevant health outcomes in PKD such as overall survival, a reduction in morbidity by improving validated quality of

life scores, or reducing complications associated with PKD and its treatments. Although increasing Hb by 1.5 g/dl and reducing transfusion burden may be beneficial, clinically relevant health outcomes in PKD is unknown at this time.

- There is no evidence directly comparing Pyrukynd (mitapivat) to any other therapy, including RBCTs with ICT, the current standard of care for PKD.

Investigational Uses [8]

- Studies of Pyrukynd (mitapivat) in various other settings are ongoing.
  - Hemolytic anemia due to PKD in the pediatric patients
  - Sickle cell anemia
  - Alpha and beta thalassemia.
- Pyrukynd (mitapivat) has only been FDA approved to treat hemolytic anemia in patients with PKD. The clinical benefit of Pyrukynd (mitapivat) for use in other conditions has not been established and is considered investigational.

Safety [6 7]

- Acute hemolysis can occur with abrupt interruption or discontinuation of therapy, and the dose should be tapered down when discontinued (see *Dosing* below).
- Pyrukynd (mitapivat) may interact with strong or moderate CYP3A4 inhibitors and P-gp inhibitors.
- Current safety information is based on very small numbers of patients who received Pyrukynd (mitapivat) for up to 40 weeks. Additional adverse effects may be identified as more safety experience is accumulated.

Dosing[7]

- Pyrukynd (mitapivat) is available in various tablet strength as 28- day treatment packs (56 tablets per pack) as well as a taper packs.
- Pyrukynd (mitapivat) should be started at a dose of 5 mg twice daily and slowly titrated up based on patients Hb levels and transfusion history (as defined in *Appendix* 2).
- The maximum dose of Pyrukynd (mitapivat) is 50 mg twice daily.
- To reduce the risk of acute hemolysis when Pyrukynd (mitapivat) is being discontinued, the dose should be tapered down gradually (as defined in *Appendix* 3).

Appendix 1: Definition of Ineffective/Not tolerated/contraindication to standard supportive PKD therapy (red blood cell transfusions and/or iron chelation therapy) [4 6 9]

- RBCT Ineffective:
  - Patient is unable to maintain a hemoglobin (Hgb) ≥ 7 g/dl, despite RBC transfusions.
  - Severe anemia symptoms despite RBCTs, such as, fatigue, shortness of breath, jaundice, bone pain, and reduced physical functioning.
- RBCT contraindication(s) or intolerance (including but not limited to):
  - Excessive volume overload, such that RBCTs are not an option.
  - Transfusion reactions, allergic, hemolytic, alloimmunization: despite management by a transfusion medicine specialist.
  - Other transfusion-related reactions: Transfusion-related lung injury (TRALI), transfusion-related graft vs. host disease (GVHD).
- ICT contraindication(s) or intolerance (including but not limited to):
  - Transfusion- or PKD-related iron overload, despite compliant use of ICT. [a]
  - Patient is intolerant of ICT or has documented contraindication to all ICT options.

[a] Defined as at least one of the following markers of iron overload: serum ferritin ≥ 1000 mg/ml, liver iron concentration > 5 mg/g, myocardial iron (T2) < 20 msecs

ICT: iron chelation therapy. Options include deferoxamine, deferasirox, or deferiprone; RBCT: red blood cell transfusion.

Appendix 2: Pyrukynd (mitapivat) upward dose titration schedule[7]		
Duration	**Dosage**	**How Supplied (NDC)**
Week 1-4	5mg twice daily.	5mg, 28-day pack (56 tablets) (71334-0205-05)
Week 5-8	If Hb is below normal range or patient has required a transfusion within the last 8 weeks: • Increase to 20mg twice daily and maintain for 4 weeks. If Hb is within normal range and patient has not required a transfusion within the last 8 weeks: • Maintain 5mg twice daily.	20mg, 28-day pack (56 tablets) (71334-0210-20)
Week 9-12	If Hb is below normal range or patient has required a transfusion within the last 8 weeks: • Increase to 50mg twice daily and maintain for 4 weeks. If Hb is within normal range and patient has not required a transfusion within the last 8 weeks: • Maintain current dose (5mg twice daily or 20mg twice daily).	50mg, 28-day pack (56 tablets) (71334-0215-50)
Maintenance	Dosing per established dose above. If Hb decreases: • May increase to the maximum of 50mg twice daily as per above schedule.	N/A

Appendix 3: Pyrukynd (mitapivat) Dose taper schedule for discontinuation [7]				
Current Dose	**Taper pack to be used for discontinuation (NDC)**	**Day 1-7**	**Days 8-14**	**Day 15 and forward**
5mg twice daily	5mg blister wallet with 7 tablets total (71334-0220-11)	5mg once daily	Discontinue	N/A
20mg twice daily	20mg and 5mg blister wallet with 14 tablets total (71334-0225-12)	20mg once daily	5mg once daily	Discontinue
50mg twice daily	50mg and 20mg blister wallet with 14 tablets total (71334-0230-13)	50mg once daily	20mg once daily	Discontinue

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Revision History

Revision Date	Revision Summary
6/5/2025	• Removed splenectomy requirement from coverage criteria. • Transfusion-dependence remains in criteria although it was removed from "not medically necessary" for administrative clarification. The intent has not changed.
6/20/2024	No criteria changes with this annual review.
6/15/2023	No changes to coverage criteria with this annual update.
6/17/2022	New Policy (effective 9/1/2022). Limits coverage of Pyrukynd (mitapivat) to genetically-confirmed transfusion-dependent PKD (as outlined in the coverage criteria), when managed by a hematologist, despite standard transfusion therapy and splenectomy, unless contraindicated.

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