

09-J4000-29

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Reviewed: 04/08/26

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Subject: Mitapivat (Pyrukynd)

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Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

On February 17, 2022, the U.S. Food and Drug Administration (FDA) Pyrukynd (mitapivat), an oral pyruvate kinase activator, for the treatment of hemolytic anemia in adults with pyruvate kinase deficiency (PKD). PKD is a rare inherited disorder believed to occur in 1 in 20,000 Caucasians. PKD is characterized by hemolytic anemia of variable severity ranging from mild anemia diagnosed in adulthood to severe transfusion-dependent anemia at birth. Pyrukynd is the first FDA-approved therapy for PKD. Prior treatments were supportive, including red blood cell transfusions, folic acid supplementation, splenectomy, and iron chelation therapy. In December 2026, Aqvesme (mitapivat) was approved for the treatment of anemia in adults with alpha- or beta-thalassemia. Aqvesme is the only approved treatment for both patient populations.

Pyruvate Kinase Deficiency

The safety and efficacy of mitapivat for PKD were evaluated in two phase 3 clinical trials: ACTIVATE (n=80) and ACTIVATE-T (n=27).

ACTIVATE (NCT03548220)

ACTIVATE was a randomized, double-blind, placebo-controlled clinical trial conducted in adults with PKD who were not regularly transfused. Included patients had at least 2 variant alleles in the PK liver and RBC (PKLR) gene (including at least 1 missense variant) and Hb 10 g/dL or less, without having had more than 4 transfusions in the past 52 weeks, and no transfusions with 3 months of enrollment. Patients who were homozygous for the c.1436G>A (p.R479H) variant or had 2 non-missense variants in the PKLR gene were excluded. Patients randomized to receive mitapivat were permitted a dose titration up to mitapivat 50 mg twice daily followed by a fixed dose for 12 weeks or placebo. Most patients in the mitapivat group (88%) were maintained on 50 mg twice daily. The median treatment duration was 24.1 weeks (range, 23.6 to 27.4 weeks).

For the primary outcome, treatment with mitapivat compared to placebo significantly improved Hb response rate (40% vs 0%); response was defined as 1.5 g/dL or greater increase in Hb from baseline and sustained at 2 or more assessments (Weeks 16, 20, and 24) and not requiring transfusions. In secondary outcomes, mitapivat treatment compared with placebo also significantly improved least squares mean change in hemoglobin compared with placebo (1.8 g/dL; 95% CI, 1.2 to 2.4 g/dL), indirect

bilirubin (-1.5 mg/dL; 95% CI, -2.2 to -0.9), reticulocyte fraction (-0.1; 95% CI, -0.14 to -0.06), lactate dehydrogenase (-71 units/L; -116 to -26 units/L), and haptoglobin (15.8 mg/dL; 95% CI, 4.3 to 27.3 mg/dL) levels. Treatment with mitapivat also reduced jaundice, tiredness, and shortness of breath from baseline compared with placebo per the daily Pyruvate Kinase Deficiency Diary.

Of the 16 patients with a Hb response in the ACTIVATE trial, 15 continued in the long term extension study and 13 maintained the Hb response at the last assessment without requiring any transfusions. The median duration of response was 6.9 months (range, 3.3 to more than 18.4 months).

ACTIVATE-T (NCT03559699)

ACTIVATE-T was a randomized, double-blind, placebo-controlled clinical trial conducted in adults with PKD who were regularly transfused. Included patients had at least 2 variant alleles in the PK liver and RBC (PKLR) gene (including at least 1 missense variant) and had a minimum of 6 transfusions in the past 52 weeks. Patients who were homozygous for the c.1436G>A (p.R479H) variant or had 2 non-missense variants in the PKLR gene were excluded. Patients received a dose titration up to mitapivat 50 mg twice daily followed by a fixed dose for 24 weeks. The median treatment duration was 40.3 weeks (range, 16.3 to 46.3 weeks).

For the primary outcome, treatment with mitapivat improved transfusion reduction response in 33% of patients (9 patients; 95% CI, 17% to 54%); response was defined as 33% or greater reduction in the number of RBC units transfused during the fixed dose period compared with historical transfusion burden. In a secondary outcome, mitapivat treatment resulted in 22% of patients (6 patients; 95% CI, 9% to 42%) who became transfusion free.

In both clinical trials, response to mitapivat occurred early in therapy, with mean increases of at least 1 mg/dL in Hb occurring by week 8.

Alpha- or Beta-Thalassemia

The safety and efficacy of mitapivat for the treatment of anemia in alpha- or beta-thalassemia were evaluated in two phase 3 clinical trials: ENERGIZE (n=194) and ENERGIZE-T (n=258).

ENERGIZE

The efficacy of mitapivat was evaluated in ENERGIZE, a multinational, randomized, double-blind, placebo-controlled clinical study (NCT04770753) of 194 adults with non-transfusion-dependent alpha- or beta-thalassemia, defined as having had no more than 5 RBC units transfused during the 24-week period prior to randomization and no RBC transfusions within 8 weeks prior to informed consent and during the screening period. Patients were included if they had a documented diagnosis of thalassemia (beta-thalassemia with or without alpha-globin gene mutations, HbE/beta-thalassemia, or alpha-thalassemia/HbH disease) and a baseline Hb concentration ≤ 10 g/dL. Randomization was stratified by baseline Hb concentrations (≤ 9 g/dL vs 9.1-10 g/dL) and thalassemia genotype (alpha-thalassemia/HbH disease vs beta-thalassemia).

Among the 194 patients with non-transfusion-dependent alpha- or beta-thalassemia, 130 patients were randomized to receive 100 mg of mitapivat twice daily during the 24-week double-blind period.

Efficacy was based upon Hb response, defined as a ≥ 1 g/dL increase in average Hb concentration from Week 12 through Week 24.

The primary outcome of proportion of patients who achieved Hb response from Week 12 through Week 24, defined as a 1 g/dL or greater increase in average Hb concentration from baseline, was significantly greater with mitapivat compared with placebo (42.3% vs 1.6%; adjusted rate difference, 40.9% [95% CI, 32% to 49.8%]).

ENERGIZE-T

The efficacy of mitapivat was evaluated in ENERGIZE-T, a multinational, randomized, double-blind, placebo-controlled clinical study (NCT04770779) of 258 adult patients with transfusion-dependent alpha-

or beta-thalassemia, defined as having had 6 to 20 RBC units transfused and no longer than a 6-week transfusion-free period during the 24 weeks prior to randomization. Patients were included if they had a documented diagnosis of thalassemia (beta-thalassemia with or without alpha-globin gene mutations, HbE/beta-thalassemia, or alpha-thalassemia/HbH disease).

Among the 258 patients with transfusion-dependent alpha- or beta-thalassemia, 171 patients were randomized to receive 100 mg of mitapivat twice daily during the 48-week double-blind period.

Efficacy was based upon transfusion reduction response, defined as $\geq 50\%$ reduction in the number of red blood cell units transfused with a reduction of at least 2 units of RBCs transfused in any consecutive 12-week period through Week 48 compared with baseline.

The primary outcome of proportion of patients who achieved transfusion reduction response was significantly greater with mitapivat compared with placebo (30.4% vs 12.6%; adjusted rate difference, 17.6% [95% CI, 8% to 27.2%]). A secondary outcome of the proportion of patients achieving at least a 50% reduction in RBC units transfused compared with baseline was significantly improved over any consecutive 24-week period (13.5% vs 2.3%) and from Week 13 through Week 48 (7.6% vs 1.1%) with mitapivat versus placebo, respectively.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of mitapivat (Pyrukynd, Aqvesme) **meets the definition of medical necessity** for the following indications when **ALL** associated criteria are met:

1. Pyruvate Kinase Deficiency (PKD)
 - a. Member's diagnosis is confirmed by **ALL** of the following – laboratory documentation must be provided:
 - i. Member has a minimum of two mutant alleles in the PKLR gene, with a least one missense mutation
 - ii. Member is not homozygous for the R479H mutation in the PKLR gene
 - iii. Member does not have two non-missense variants in the PKLR gene without the presence of another missense variant
 - b. Member meets one of the following:
 - i. Member has required a minimum of 6 transfusions within the past year – documentation from the medical record must be provided
 - ii. Member has required a maximum of 4 transfusions within the past year and has not had any transfusions in the past three months AND hemoglobin level is currently (within the most recent 3 months) less than or equal to 10 mg/dL – laboratory documentation must be provided
 - c. Mitapivat is prescribed by, or in consultation with, a hematologist, nephrologist, or other specialist with expertise in the treatment of PKD
 - d. Dose does not exceed:
 - i. Initial: 5 mg twice daily
 - ii. Maintenance: 50 mg twice daily – the fewest number of tablets must be used

2. Alpha- or Beta-thalassemia

- a. Member's diagnosis is confirmed by the following:
 - i. Alpha-thalassemia
 1. Biallelic pathogenic variants in both HBA1 and HBA2 that result in deletion or inactivation of all four α -globin alleles (---) – laboratory documentation must be provided:
 2. Biallelic pathogenic variants in HBA1 and HBA2 that result in deletion or inactivation of three α -globin alleles (--- α) – laboratory documentation must be provided
 - ii. Beta-thalassemia (may include hemoglobin E/beta thalassemia and beta-thalassemia with mutation and/or multiplication of alpha globin)
 1. Biallelic pathogenic (or likely pathogenic) variants in HBB – laboratory documentation must be provided
- b. One of the following:
 - i. Member is transfusion-dependent as evidenced by receiving six or more red blood cell units transfused over a 24 week period – documentation from the medical record must be provided
 - ii. Member's Hb concentration is less than or equal to 10.0 grams per deciliter (g/dL) (100 grams per liter [g/L]), based on an average of at least 2 Hb concentration measurements (separated by ≥ 7 days) – laboratory documentation must be provided
- c. Mitapivat will not be used in combination with luspatercept-aamt (Reblozyl)
- d. Member has NOT previously received gene therapy (including betibeglogene autotemcel [Zynteglo], exagamglogene autotemcel [Casgevy]) OR an allogenic HSCT in their lifetime
- e. Mitapivat is prescribed by, or in consultation with, a hematologist or other specialist with expertise in the treatment of alpha- or beta-thalassemia
- f. Dose does not exceed 100 mg twice daily – the fewest number of tablets must be used

Approval duration: 6 months

Continuation of mitapivat (Pyrukynd, Aqvesme) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Authorization/reauthorization has been previously approved by Florida Blue or another health plan in the past two years for treatment of PKD, alpha-thalassemia, beta-thalassemia, **OR** the member has previously met all indication-specific criteria.
2. Member's diagnosis is confirmed by the following:
 - a. PKD
 - i. Member has a minimum of two mutant alleles in the PKLR gene, with a least one missense mutation – laboratory documentation must be provided
 - ii. Member is not homozygous for the R479H mutation in the PKLR gene – laboratory documentation must be provided
 - iii. Member does not have two non-missense variants in the PKLR gene without the presence of another missense variant – laboratory documentation must be provided
 - b. Alpha-thalassemia

1. Biallelic pathogenic variants in both HBA1 and HBA2 that result in deletion or inactivation of all four α -globin alleles (--/--) – laboratory documentation must be provided:
2. Biallelic pathogenic variants in HBA1 and HBA2 that result in deletion or inactivation of three α -globin alleles (--/- α) – laboratory documentation must be provided
- c. Beta-thalassemia (may include hemoglobin E/beta thalassemia and beta-thalassemia with mutation and/or multiplication of alpha globin)
 - i. Biallelic pathogenic (or likely pathogenic) variants in HBB – laboratory documentation must be provided Alpha- or beta-thalassemia
3. Member demonstrates a beneficial response to treatment with mitapivat, as evidenced by one of the following:
 - a. Indication for use is PKD AND member has a reduction in number of transfusions since starting treatment with mitapivat or maintains a prior reduction in number of transfusions – documentation from the medical record must be provided
 - b. Indication for use is alpha- or beta-thalassemia and one of the following:
 - i. Member has a reduction in number of transfusions since starting treatment with mitapivat or maintains a prior reduction in number of transfusions – documentation from the medical record must be provided
 - ii. Member has a minimum 1 g/dL increase or more in average Hb concentration compared to baseline (prior to treatment with mitapivat) – laboratory documentation must be provided
4. Mitapivat is prescribed by (or in consultation with) a hematologist, nephrologist, or other specialist with expertise in the treatment of PKD, alpha-thalassemia, or beta-thalassemia
5. Dose does not exceed:
 - a. PKD: 50 mg twice daily – the fewest number of tablets must be used
 - b. Alpha- or beta-thalassemia: 100 mg twice daily – the fewest number of tablets must be used

Approval duration: 6 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- PKD:
 - 5 mg orally twice daily
 - Titrate from 5 mg twice daily to 20 mg twice daily, and then to the maximum recommended dose of 50 mg twice daily with dose increases occurring every 4 weeks
 - Discontinue if no benefit has been observed by 24 weeks, based on the hemoglobin and hemolysis laboratory results and transfusion requirements
- Alpha- or beta-thalassemia: 100 mg twice daily

Dose Adjustments

- Avoid use in moderate or severe hepatic impairment
- Avoid co-administration of strong CYP3A inhibitors and strong CYP3A inducers
- Do not titrate beyond 20 mg twice daily if administered with moderate CYP3A inhibitors

Drug Availability

- Pyrukynd:
 - Tablets: 5 mg, 20 mg, and 50 mg
- Aqvesme:
 - Tablets: 100 mg

PRECAUTIONS:

Boxed Warning

- Hepatocellular injury

Contraindications

- None

Precautions/Warnings

- Acute Hemolysis

BILLING/CODING INFORMATION:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified
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ICD-10 Diagnosis Codes That Support Medical Necessity

D55.21	Anemia due to pyruvate kinase deficiency
D56.0	Alpha thalassemia
D56.1	Beta thalassemia

REIMBURSEMENT INFORMATION:

Refer to section entitled [POSITION STATEMENT](#).

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at [Coverage Protocol Exemption Request](#).

DEFINITIONS:

None.

RELATED GUIDELINES:

None.

OTHER:

None.

REFERENCES:

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 04/08/26.

GUIDELINE UPDATE INFORMATION:

07/01/22	New Medical Coverage Guideline.
03/15/23	Revised Position Statement.
05/15/24	Review and revision to guideline; updated position statement and references
07/15/24	Revision to guideline; updated position statement.
05/15/25	Review and revision to guideline; updated position statement and references
03/15/26	Revision to guideline; updated position statement, description, dosing, warnings; addition of new product Aqvsme.
05/15/26	Review and revision to guideline; updated coding and references.