09-J4000-29

Original Effective Date: 07/01/22

Reviewed: 04/10/24

Revised: 07/15/24

Subject: Mitapivat (Pyrukynd)

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

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.

The safety and efficacy of mitapivat 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.

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) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member is diagnosed with pyruvate kinase deficiency (PKD)
2. Member meets **ALL** of the following regarding the PKLR gene – laboratory documentation must be provided:

a. Member has a minimum of two mutant alleles in the PKLR gene, with a least one missense mutation
b. Member is not homozygous for the R479H mutation in the PKLR gene
c. Member does not have two non-missense variants in the PKLR gene without the presence of another missense variant

3. Member meets one of the following:
    a. Member has required a minimum of 6 transfusions within the past year – documentation from the medical record must be provided
    b. 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
4. Mitapivat is prescribed by a nephrologist or a provider specializing in PKD
5. Dose does not exceed:
    a. Initial: 5 mg twice daily
    b. Maintenance: 50 mg twice daily – the fewest number of tablets must be used

Approval duration: 6 months

Continuation of mitapivat (Pyrukynd) **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, **OR** the member has previously met all indication-specific criteria.
2. Member meets ALL of the following regarding the PKLR gene – laboratory documentation must be provided:
    a. Member has a minimum of two mutant alleles in the PKLR gene, with a least one missense mutation
    b. Member is not homozygous for the R479H mutation in the PKLR gene
    c. Member does not have two non-missense variants in the PKLR gene without the presence of another missense variant
3. 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
4. Dose does not exceed 50 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

- 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

Dose Adjustments

- Avoid use in moderate or severe hepatic impairment
- Avoid co-administration of strong CYP3A inhibitors and strong CYP3A inducers
- Do no titrate beyond 20 mg twice daily if administered with moderate CYP3A inhibitors

Drug Availability

- Tablets: 5 mg, 20 mg, and 50 mg

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- Acute Hemolysis

BILLING/CODING INFORMATION:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified

ICD-10 Diagnosis Codes That Support Medical Necessity

D55.21	Anemia due to pyruvate kinase deficiency

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.

DEFINITIONS:

None.

RELATED GUIDELINES:

None.

OTHER:

None.

REFERENCES:

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8. Rab MAE, Van Oirschot BA, Kosinski PA, et al. AG-348 (Mitapivat), an allosteric activator of red blood cell pyruvate kinase, increases enzymatic activity, protein stability, and ATP levels over a broad range of PKLR genotypes. Haematologica. 2021 Jan 1;106(1):238-249. doi: 10.3324/haematol.2019.238865.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 04/10/24.

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.