mitapivat (Pyrukynd®)

EOCCO POLICY

Policy Type:PA/SP Pharmacy Coverage Policy: EOCCO255

Description

Mitapivat (Pyrukynd) is an orally administered pyruvate kinase activator.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
mitapivat (Pyrukynd)	Hemolytic anemia in patients with pyruvate kinase deficiency	5 mg tablets	56 tablets/28 days
		20 mg tablets	
		50 mg tablets	
		5 mg tablet taper pack	7 tablets/7 days*
		20 mg and 5 mg taper pack	14 tablets/14 days*
		50 mg and 20 mg taper pack	14 tablets/14 days*

**In patients established on treatment and are discontinuing treatment, one fill of one of the taper packs will be allowed.*

Initial Evaluation

I. **Mitapivat (Pyrukynd)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by a hematologist; **AND**
   C. A diagnosis of **pyruvate kinase deficiency (PKD)** when the following are met:
      1. Provider attestation to all of the following;
         i. Diagnosis is confirmed via genetic testing (documentation of results required); **AND**
         ii. Presence of two mutant alleles in the PKLR gene; **AND**
         iii. At least one missense mutation (i.e., presence of two non-missense mutations does not qualify for therapy); **AND**
         iv. Member is NOT homozygous for the R479H mutation; **AND**
      2. Hemoglobin level is less than 10 mg/dL, measured within the past three months; **AND**
      3. Documentation of baseline hemoglobin level (for renewal assessment); **AND**
      4. Member has symptoms of hemolytic anemia (e.g., fatigue, weakness, dizziness, jaundice) that negatively impact quality of life; **AND**

5. The member has been regularly transfused or transfusion-dependent for at least 12 months (e.g., five or more blood transfusions over the past year); **OR**
    i. The member is unable to tolerate blood transfusions and/or is not a candidate for blood transfusions. Documentation of rationale required.

II. Mitapivat (Pyrukynd) is considered not medically necessary when criteria above are not met and/or when used for:
    A. Patients with pyruvate kinase deficiency that have two non-missense mutations or are homozygous for R479H mutation.
    B. Hemolytic anemia in patients with PKD that do not have symptoms or symptoms severe enough to impact quality of life.

III. Mitapivat (Pyrukynd) is considered investigational when used for all other conditions, including but not limited to:
    A. Pediatric patients with PKD
    B. Sickle cell disease
    C. Thalassemia

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Documentation that hemoglobin level (measured within the past three months) has increased compared to baseline; **AND**
IV. Documentation that the member's symptoms have improved compared to baseline.

Supporting Evidence

I. Mitapivat (Pyrukynd) is a pyruvate kinase (PK) activator for hemolytic anemia in adults with PKD. Safety and efficacy have not been established in pediatrics, but ongoing clinical trials are evaluating. Evidence for use is limited to a small adult-only population; it is unknown if the results are applicable to pediatrics. Pediatrics utilizing mitapivat (Pyrukynd) are best monitored under a clinical trial setting until therapy is FDA-approved for patients under the age of 18.

II. Individuals with PKD have two PKLR gene mutations, either homozygous for a single mutation or compound heterozygotes for two different mutations. Individuals with one mutation are generally not affected by PKD symptoms and do not require treatment. Mitapivat (Pyrukynd) has not been evaluated and has unknown clinical value in this population.

III. Diagnostics for PKD include biochemical measurement of red blood cell PK activity, and genetic testing. PKD is rare and may be misdiagnosed. Additionally, in clinical trials patients homozygous for R479H or those with two non-missense mutations did not respond to treatment. Thus, genetic testing is required to determine appropriate diagnosis with responsive mutations prior to coverage consideration. Agios Pharmaceuticals Inc. offers a complimentary genetic test. Biochemical testing (e.g., PK activity, etc.) is insufficient to determine a diagnosis of PKD, and does not provide present mutations. Given the genetic, symptomatic, and management complexities of this condition, prescription by a specialist provider is required.

IV. PKD management is based on symptom severity, which varies between patients even when Hb levels are comparable. When patients are experiencing symptoms that impact quality of life (QOL), supportive management/treatment may be warranted. Management strategies include:

- Blood transfusions, often coupled with iron chelation therapy to prevent iron overload.
- Splenectomy, which may reduce transfusion burden and improve symptoms; however, is not curative. Optimal timing of splenectomy is between 5-18 years of age given risks.
- Folic acid may be administered in those with a deficiency.

V. The National Cancer Institute classified anemia into five grades: Grade 1 (mild): hemoglobin (Hb) of 10 g/dL to the lower limit of normal for member age and gender, Grade 2 (moderate): Hb between 8-10 g/dL, Grade 3 (severe), Grade 4 (life-threatening), and Grade 5 is death. Mitapivat (Pyrukynd) was evaluated in patients with a Hb of 10 g/dL or less (i.e., at least moderate anemia), and this is the patient population expected to have symptoms that negatively impact QOL. Unmanaged patients with Hb above 10 g/dL are near normal levels and unlikely require treatment. A Hb level measured within the past three months is required to ensure treatment is appropriate. Documentation of baseline Hb is required upon initiation to determine objective therapeutic effect upon renewal. Not all patients in clinical trials responded to treatment. Additionally, documented symptom response is required given that PKD is managed/treated on the basis of symptoms and not target Hb levels, especially as positive long-term impact on the disease has not been demonstrated for this therapy. In absence of patient-reported symptom improvement, use of mitapivat (Pyrukynd) should not be continued.

VI. Mitapivat (Pyrukynd) was evaluated in two Phase 3 trials. Objective hematopoiesis measures and subjective patient reported outcomes (PROs) were evaluated. The Pyruvate Kinase Deficiency Diary (PKDD) and the Pyruvate Kinase Deficiency Impact assessment (PKDIA) measure daily signs of symptoms of PKD and impact on daily social and physical activities, respectively. Meaningful changes are predicted to be 5-8 points for PKDD and 6-10 points for PKDIA.

- ACTIVATE-T: Single-arm trial, over 24 weeks in regularly transfused patients (≥ 6/year). Baseline Hb: 9.1 g/dL. Outcomes: proportion of patients with transfusion response (33%

reduction in transfusion burden), transfusion-free patients, and those achieving a normal Hb. Nine patients (33%) met transfusion response, 6 (22%) became transfusion-free, and 3 (11%) achieved normal Hb levels. Although not powered or evaluated for significance, the average PKDD average score decreased by -2.4 points (baseline was 51.9), and the PKDIA score decreased by -9.1 on average (baseline 52.6).

- ACTIVATE: An open-label, placebo-controlled trial over 12 weeks in patients not regularly transfused (≤ 4/year). Baseline Hb was 8.5-8.6 g/dL. Outcomes: Hb response (Hb change of ≥ 1.5 g/dL), and PROs. Hb response was seen in 16 (40%) of patients on mitapivat (Pyrukynd) vs. no patients in the placebo group, and the average change in Hb was +1.7 g/dL compared to -0.1 g/dL for the placebo group, both of which were statistically and clinically significant. The PKDD score at week 24 had decreased by 5.16 points on average compared to baseline for mitapivat (Pyrukynd) which was statistically significant over placebo. The PKDIA scores reached statistical superiority over placebo but did not meet clinically relevant thresholds.

VII. In ACTIVATE, serious adverse events (AE) occurred in 10% of patients on mitapivat (Pyrukynd), including atrial fibrillation, gastroenteritis, rib fracture, musculoskeletal pain. Common AE that occurred in at least 5% of patients and higher than placebo included decrease estrone (56%) and decreased estradiol (12%) in males only, increased urate, back pain, arthralgia, dyslipidemia, gastroenteritis, hot flush, oropharyngeal pain, hypertension, arrhythmia, breast discomfort, constipation, dry mouth and paresthesia. Around 155 patients have been treated with mitapivat (Pyrukynd) to date; thus, the full safety profile is likely not well understood.

VIII. Transfusions may place a high burden on patients. In the ASH publication, Management of Pyruvate Kinase Deficiency in Children and Adults (Grace, Barcellini, 2020), regularly transfused patients are those that receive six or more transfusions per year, where those that are not regularly transfused are those that have received four or fewer. Mitapivat (Pyrukynd) has shown to increase Hb levels and reduce transfusion burden, likely providing clinical value in those that have a high-transfusion burden, need treatment but are unable to tolerate transfusions (e.g., previous immune or hemolytic transfusion reaction), or where risks of transfusion outweigh the benefits. Long term implications on patient-perceived burden of disease, improved survival, positive impacts on bone mineral density, prevention of iron overload, etc. have not been shown. Furthermore, very few patients in the clinical trials were able to become transfusion-free. It is likely that transfusions will need to be continued in some capacity for most patients even after starting mitapivat (Pyrukynd). Mitapivat (Pyrukynd) has questionable value over transfusions in those that could be managed with transfusions intermittently. In the not regularly transfused population, improvement in markers of hemolysis and Hb were seen; however Hb level is not strongly correlated with symptom severity and thus need for treatment. The PKDD diary assessment met the minimally important clinical change; however, PKDIA scores, which measure QOL and physical functioning, did not meet clinically meaningful thresholds. In summary, mitapivat (Pyrukynd) may be a valuable therapy in those that are not

candidates for current management strategies or where transfusion-burden is high. Therapy is determined as medically necessary in those beyond the definition of not regularly transfused (i.e., those eligible are those with five or more transfusions over the past year).

IX. In clinical trials, increases in Hb occurred rapidly in responders, with average increases in Hb by week eight of therapy. The max dose will be reached by the start of the third month; thus, a three-month initial duration of approval is sufficient to determine treatment response. Thereafter, Hb level within the past three months is required to confirm continued treatment benefit. In clinical trials not all patients responded to therapy or responded long-term. In the long-term extension trial, duration of response up to 19.5 months occurred in some patients, but many patients do not have extended duration of response. When subjective response or objective Hb response lapse, therapy should be discontinued.

Investigational or Not Medically Necessary Uses

I. Mitapivat (Pyrukynd) is considered not medically necessary:
   A. For patients with pyruvate kinase deficiency that have two non-missense mutations or are homozygous for R479H mutation. In a Phase 2, DRIVE-PK study of mitapivat (Pyrukynd) patients with these mutational characteristics were non-responders. Thus, the pivotal Phase 3 trials excluded these patients from enrollment.
   B. For patients that are not experiencing symptoms severe enough to impact QOL. Decision to treat in PKD is based on symptom severity, rather than objective markers (e.g., Hb). The currently known value of mitapivat (Pyrukynd) is to improve symptoms of disease by increasing Hb. There are no data to show an impact on long-term outcomes of disease.

II. Mitapivat (Pyrukynd) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below. Clinical trials are underway to investigate:
   A. Pediatric patients with PKD
   B. Sickle cell disease
   C. Thalassemia

References

1. Grace RF, Rose C, Layton DM, et al. Safety and efficacy of mitapivat in pyruvate kinase deficiency. New England Journal of Medicine. 2019;381(10):933-944.
2. Pyrukynd [Prescribing Information]. Agios Pharmaceuticals Inc. Cambridge, MA. February 2022.
3. Agios Pharmaceuticals, Inc. A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ag-348 in Not Regularly Transfused Adult Subjects with Pyruvate Kinase Deficiency. clinicaltrials.gov; 2020.
4. Agios Pharmaceuticals, Inc. An Open-Label Study to Evaluate the Efficacy and Safety of Ag-348 in Regularly Transfused Adult Subjects with Pyruvate Kinase (Pk) Deficiency. clinicaltrials.gov; 2021.

5. Grace RF, Barcellini W. Management of pyruvate kinase deficiency in children and adults. Blood. 2020;136(11):1241-1249.

Related Policies

There are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2022