PYRUKYND (PREAUTHORIZATION REQUIRED)

X.196

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POLICY

TARGET AGENT(S)

Pyrukynd® (mitapivat) is FDA approved:

- For the treatment of hemolytic anemia in adults with pyruvate kinase (PK) deficiency.

Brand (generic)	GPI (NDC)	Multisource Code	Quantity Limit (per day or as listed)
Pyrukynd (mitapivat)			
Pyrukynd 5mg Taper Pack	8587005070B710	M, N, O, or Y	
Pyrukynd 20mg&5mg Taper Pack	8587005070B720	M, N, O, or Y	
Pyrukynd 50mg&20mg Taper Pack	8587005070B735	M, N, O, or Y	
20mg tablet	85870050700325	M, N, O, or Y	2
5mg tablet	85870050700310	M, N, O, or Y	3
50mg tablet	85870050700340	M, N, O, or Y	2

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

BlueCross BlueShield Nebraska

following are met:

A. The patient has a diagnosis of hemolytic anemia with pyruvate kinase deficiency (PKD) as confirmed by genetic testing showing a pathogenic PKLR gene mutation and **ALL** of the following:

1. The patient is **NOT** homozygous for the c.1436Ggreater than A (p.R479H) variant **AND**
2. The patient has at least 2 variant alleles in the PKLR gene, of which at least 1 is a missense variant **AND**
3. The patient has at least 2 variant alleles in the PKLR gene, of which at least 1 is a missense variant

AND

B. **ONE** of the following:

1. The patient has a hemoglobin of less than or equal to 10g/dL **OR**
2. The patient had had more than 4 red blood cell (RBC) transfusions in the past year

AND

C. **ONE** of the following:

1. The patient will be using folic acid at a dose of at least 0.8 mg daily in combination with the requested agent **OR**
2. The patient has an intolerance, hypersensitivity, or FDA labeled contraindication to folic acid therapy

AND

D. **ONE** of the following:

1. The patient's age is within FDA labeling for the requested indication for the requested agent **OR**

AND

E. The prescriber is a specialist in the area of the patient's diagnosis (e.g., hematologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis

AND

F. The patient does **NOT** have any FDA labeled contraindications to the requested agent **AND**

G. **ONE** of the following:

1. The requested quantity (dose) does **NOT** exceed the program quantity limit **OR**

2. **ALL** of the following:

a. The requested quantity (dose) is greater than the program quantity limit **AND**

b. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND**

c. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

Length of Approval: 6 months

Renewal Evaluation

I. Target agent(s) **may be considered medically necessary** when **ALL** of the following are met:

A. The patient has been previously approved for the requested agent through the plan's Prior Authorization process **AND**

AND

C. The prescriber is a specialist in the area of the patient's diagnosis (e.g., hematologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND**

D. **ONE** of the following:

a. The patient will be using folic acid at a dose of at least 0.8 mg daily in combination with the requested agent **OR**

b. The patient has an intolerance, hypersensitivity, or FDA labeled contraindication to folic acid therapy

AND

E. The patient does **NOT** have any FDA labeled contraindications to the requested agent **AND**

F. **ONE** of the following:

a. The requested quantity (dose) does NOT exceed the program quantity limit **OR**

b. **ALL** of the following:

i. The requested quantity (dose) is greater than the program quantity limit **AND**

ii. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND**

iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

Length of Approval: 12 months

Last Review
08-09-2023
Next Review
05-10-2025

CLINICAL RATIONALE

Pyruvate kinase deficiency (PKD) is the most common enzyme-related glycolytic defect that results in red cell hemolysis. PKD is characterized by clinical heterogeneity. Heterogeneity results in a variable degree of hemolysis, causing irreversible cellular disruption. Invariably, PKD results in hereditary non-spherocytic anemia. Manifestations occur from the neonatal period through adult life.

Red blood cell (RBC) metabolism hinges on glycolysis. Pyruvate kinase (PK) enzyme is key to this process. PK converts phosphoenolpyruvate to pyruvate. This step yields 50% of RBC ATP. PK modulates NADH production for methemoglobin reduction. These metabolites enable RBCs to function effectively. In PKD, cellular energy efficiency and longevity decrease. Young RBCs are most affected in PKD. PK expression is controlled by the PK-LR gene. PKD follows an autosomal recessive inheritance pattern.(2)

Cellular integrity of RBCs is maintained by membrane-bound ATPases. ATPases exchange sodium for potassium. This maintains transcellular electrochemical neutrality, cellular fluid balance, and deformability. Lack of PK enzyme decreases RBC ATP production, causing decreased RBC deformability. Intracellular potassium and water loss also occur. This results in RBC damage. PKD manifests with enzyme levels of less than 25%. Splenic and hepatic capillaries trap defective RBCs. Extravascular hemolysis occurs, causing hepatosplenomegaly. Intravascular hemolysis may also occur, causing hemoglobinuria. Anemia underlies the progressive fatigue in PKD. Increased 2,3-diphosphoglycerate (2.3-DPG) causes oxygen unloading in tissues. This shifts the oxygen dissociation curve rightward. Elevated 2,3-DPG helps compensate for anemia.(2)

Testing for PK deficiency can be done by measuring PK activity in RBCs (biochemical testing) and/or by identifying a pathogenic PKLR gene mutation (genetic testing). The most direct evidence of functional PK deficiency is by biochemical testing, unless the patient had had a recent transfusion since the transfused RBCs will have normal activity and can make the patient’s results appear normal.

The diagnosis of PKD is confirmed in a patient with hemolytic anemia (or compensated hemolysis) who has laboratory evidence of reduced RBC PK enzymatic activity and/or genetic evidence or pathogenic PKLR mutations.(3)

Iron overload is a risk in PKD. Regular screening with iron studies may reveal its onset. Hyperferritinemia may herald the onset of iron overload. Magnetic resonance imaging (MRI) for hemosiderosis is useful in selected patients.

Supportive therapy is important in chronic anemia. Folic acid supplementation is advocated for children. Pregnancy and hemolytic crises also warrant supplementation. These states are associated with increased folate demand. Blood transfusion ameliorates anemia. Decisions for transfusion must be justifiable.(2)

Splenectomy is indicated for massive splenomegaly. This eliminates the risk of traumatic rupture. Severe anemia may also benefit from splenectomy. Total splenectomy is advocated in late childhood.(2)

Hemosiderosis requires iron-chelation therapy with deferoxamine.

Treatment of PK deficiency depends on the age when the disorder becomes evident.(3)

- Before birth – fetal hydrops due to severe anemia may require intrauterine transfusion
- Neonatal period – hyperbilirubinemia during the neonatal period may necessitate phototherapy or exchange transfusion
- Infancy through adulthood – severe anemia in infants, children, and adults may require once or more of the following:
    - RBC transfusions
    - Folic acid
    - Mitapivat
    - Splenectomy
    - Iron chelation
    - Investigational therapies such as hematopoietic stem cell transplant, gene therapy, or gene editing

The efficacy of Pyrukynd was evaluated in ACTIVATE, a multinational, randomized, double-blind, placebo-controlled clinical study (NCT03548220) of 80 adults with PKD who were not regularly transfused, defined as having had no

kinase liver and red blood cell (PKLR) gene, of which at least 1 was a missense variant and Hb less than or equal to 10g/dL. Patients who were homozygous for the c1436Ggreater than A (p.R479H) variant or had 2 non-missense variants (without the presence of another missense variant) in the PKLR gene were excluded because these patients did not achieve Hb response (change from baseline in Hb greater than or equal to 1.5 g/dL at great than 50% of assessments) in the dose-ranging study.

Efficacy was based upon Hb response, defined as a greater than or equal to 1.5 g/dL increase in Hb from baseline sustained at 2 por more scheduled assessments (Weeks 16, 20, and 24) during the fixed dose period without transfusions. In ACTIVATE, the LS Mean change form baseline with Pyrukynd compared to placebo was -0.4 (standard error [SE] 0.1) for jaundice (scale: 0-4), -1.1 (SE 0.4) for tiredness (scale: 0-10), and -0.3 (SE 0.3) for shortness of breath (scale: 0-10), assessed with the daily Pyruvate Kinase Deficiency Diary (PKDD) where lower scores represent less sign/symptom severity.

In ACTIVATE, the majority of Pyrukynd-treated patients experienced an increase in Hb, while the majority of patients in the placebo arm experienced a decrease in Hb as measured by average change from baseline at Weeks 16, 20, and 24. 40% of patients in the Pyrukynd arm met the Hb response rate and 0% of patients in the placebo arm met the Hb response rate (p-value less than 0.0001).

The efficacy of Pyrukynd in patients with PK deficiency who were regularly transfused was evaluated in ACTIVATE-T, a multinational single-arm clinical trial (NCT03559699) of 27 adults with PK deficiency who had a minimum of 6 transfusion episodes in the 52-week period prior to informed consent. Patients were included if they had documented presence of at least 2 variant alleles in the PKLR gene, of which at least 1 was a missense variant. Patients who were homozygous for the (p.R479H) variant or had 2 non-missense variants (without the presence of another missense variant) in the PKLR gene were excluded.

Efficacy was based on transfusion reduction response and was defined as greater than or equal to 33% reduction in the number of red blood cell (RBC) units transfused during the fixed dose period compared with the patient's historical transfusion burden. 33% of patients (95% CI) met the transfusion reduction response endpoint and 22% (95% CI) of patients were transfusion free.

Safety

REFERENCES

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Pyrukynd Prescribing Information. Agios Pharmaceuticals, Inc. February 2022

2021

Enegela OA, Anjum F. Pyruvate Kinase Deficiency. [Updated 2021 Dec 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560581/

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Prchal JT. UpToDate Pyruvate kinase deficiency. Literature review current through February 2022.

REVISIONS

12-06-2023

Policy reviewed at Medical Policy Committee meeting on 11/8/2023 – no changes to policy