Pyrukynd (mitapivat) Prior Authorization with Quantity Limit Program Summary

This program applies to FlexRx Closed, FlexRx Open, FocusRx, GenRx Closed, GenRx Open, Health Insurance Marketplace, and KeyRx formularies.

This is a FlexRx Standard and GenRx Standard program.

POLICY REVIEW CYCLE

Effective Date	Date of Origin
8/1/2023	9/1/2022

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Pyrukynd® (mitapivat) Tablet	Treatment of hemolytic anemia in adults with pyruvate kinase (PK) deficiency		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Pyruvate kinase deficiency	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.(2) 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 has had a recent transfusion since the transfused RBCs will have normal activity and can make the patient's results appear normal.(3)
	
	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)
	
	The differential diagnoses of PKD include other causes of hemolytic anemia. Immune hemolysis and enzyme deficiencies are considerations. Antibody-mediated hemolysis occurs with blood-group incompatibility.(2)
	
	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.(2)
	
	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 (the accumulation of iron in the organs) requires iron-chelation therapy with deferoxamine.
	
	Current guidelines for PKD principally focus on supportive, rather than curative treatment of the disease. After a definitive diagnosis is established by qualitative and quantitative reduction in enzyme activity and a positive finding of homozygous or heterozygous gene mutations in the PKLR gene, patients are put into supportive care which constitutes the following framework:(3)
	
	• Folic acid supplementation
	  ○ Daily folic acid supplementation recommended in patients with moderate hemolysis, or with mild hemolysis coupled with a restricted diet to maintain effective erythropoiesis
	• Red cell transfusions
	  ○ These should be specified for each patient after a meticulous assessment of their tolerance regarding anemia, quality of life, and

	physical activity, rather than a measure of their absolute hemoglobin levels. Further assessment after each transfusion is also required • Splenectomy is the definitive treatment in those who are severely anemic or receive regular transfusions and in those at risk of splenic rupture ○ Indicated between the age of 5 year to before adolescence
Efficacy(1)	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 more than 4 transfusions in the 52-week period prior to treatment and no transfusion in the 3-month period prior to treatment. Patients were included if they had documented presence of at least 2 variant alleles in the pyruvate 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 c1436G > 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 or 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 c1436G > A (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(1)	Pyrukynd (mitapivat) has no known FDA labeled contraindications.

REFERENCES

Number	Reference
1	Pyrukynd Prescribing Information. Agios Pharmaceuticals, Inc. February 2022.
2	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/
3	Iqbal A, Habiba U, Waseem R, Islam Z. Pyruvate kinase activator: A major breakthrough in the world of Hematology. Ann Med Surg (Lond). 2022 Sep 14;82:104631. doi: 10.1016/j.amsu.2022.104631. PMID: 36268365; PMCID: PMC9577647.

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Pyrukynd	mitapivat sulfate tab	20 MG ; 5 MG ; 50 MG	M ; N ; O ; Y	N		
Pyrukynd taper pack	mitapivat sulfate tab therapy pack	5 MG ; 7 x 20 MG & 7 x 5 MG ; 7 x 50 MG & 7 x 20 MG	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Pyrukynd	Mitapivat Sulfate Tab	5 MG	56	Tablets	28	DAYS			
Pyrukynd	Mitapivat Sulfate Tab	20 MG	56	Tablets	28	DAYS			
Pyrukynd	Mitapivat Sulfate Tab	50 MG	56	Tablets	28	DAYS			
Pyrukynd taper pack	Mitapivat Sulfate Tab Therapy Pack	5 MG	7	Tablets	365	DAYS			
Pyrukynd taper pack	Mitapivat Sulfate Tab Therapy Pack	7 x 20 MG & 7 x 5 MG	14	Tablets	365	DAYS			
Pyrukynd taper pack	Mitapivat Sulfate Tab Therapy Pack	7 x 50 MG & 7 x 20 MG	14	Tablets	365	DAYS			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Pyrukynd	mitapivat sulfate tab	20 MG ; 5 MG ; 50 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Pyrukynd taper pack	mitapivat sulfate tab therapy pack	5 MG ; 7 x 20 MG & 7 x 5 MG ; 7 x 50 MG & 7 x 20 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Pyrukynd	Mitapivat Sulfate Tab	50 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Pyrukynd	Mitapivat Sulfate Tab	20 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
			Marketplace/BasicRx ; KeyRx
Pyrukynd	Mitapivat Sulfate Tab	5 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Pyrukynd taper pack	Mitapivat Sulfate Tab Therapy Pack	5 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Pyrukynd taper pack	Mitapivat Sulfate Tab Therapy Pack	7 x 50 MG & 7 x 20 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Pyrukynd taper pack	Mitapivat Sulfate Tab Therapy Pack	7 x 20 MG & 7 x 5 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. 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** 2. The patient is NOT homozygous for the c.1436G > A (p.R479H) 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** 4. ONE of the following: A. The patient has a hemoglobin of less than or equal to 10g/dL **OR** B. The patient has had more than 4 red blood cell (RBC) transfusions in the past year **AND** 5. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication **AND** 6. 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** 7. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 6 months NOTE: If Quantity Limit applies, please see Quantity Limit criteria **Renewal Evaluation**

Module	Clinical Criteria for Approval
	Target Agent(s) will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process **AND** 2. The patient has had clinical benefit with the requested agent (e.g., hemoglobin has increased or is within normal range, decrease in red blood cell transfusion burden) **AND** 3. 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** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please see Quantity Limit criteria

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity Limit for the requested agent will be met when ONE of the following is met: 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:** Initial - 6 months Renewal - 12 months