NEW DRUG APPROVAL

Brand Name	Pyrukynd®
Generic Name	mitapivat
Drug Manufacturer	Agios Pharmaceuticals, Inc.

New Drug Approval

FDA approval date: February 17, 2022

Review designation: Priority; Orphan

Type of review: Type 1 - New Molecular Entity; New Drug Application (NDA)**:** 216196

Dispensing restriction: Limited Distribution; Specialty Only

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Pyruvate kinase deficiency (PKD) is the most common enzyme-related glycolytic defect that results in red cell hemolysis. This disorder 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. A myriad of complications could arise from hemolytic anemia.

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. The gene is located on chromosome 1q21. PKD follows an autosomal recessive inheritance pattern. Homozygotes and compound heterozygotes are affected. Compound heterozygotes inherit two different mutant alleles. About 300 PKD-causing mutations to have been found. The majority of these are missense mutations. However, novel mutations have been reported. Frameshift, deletion, and insertion type mutations can occur.

Older children may present with poor growth, easy fatiguability, and jaundice. Some children may have poor appetite and dizziness. Stress may precipitate hemolytic crises. Physical examination shows icterus and conjunctival pallor. Hepatosplenomegaly due to hemolysis occurs. Extramedullary hemopoiesis may result in frontal bossing. Adults may present with complications. These include gall stones, hemosiderosis, and aplastic anemia.

PKD is a rare disorder. The true prevalence of PKD is unknown. Estimated PKD prevalence ranges from 3.2 - 8.5 cases per million of the Western population. However, a prevalence of 1:20,000 has been reported. Mutant allele frequency may approach 51 per million. Case clusters are found in Brazil and Tunisia. Evidence of PKD-related gender differences appears scarce. Specific mutations have higher frequencies in certain communities, such as Pennsylvania Amish and Romani communities. Certain factors could explain this finding. A founder effect indicates the heritability of mutations. Mutations have been traced to specific migrant couples. In addition, consanguinity increases the risk of homozygosity.

Efficacy

Table 1. ACTIVATE (NCT03548220) and ACTIVATE-T (NCT03559699) Clinical Trial Description

	ACTIVATE (N = 80)	ACTIVATE-T (N = 27)
Study Design	Randomized, double-blind, placebo-controlled	Single-arm, open-label
Inclusion Criteria	• Patients 18 years of age and older with PKD and at least 2 mutant alleles in the *PKLR* gene, of which at least 1 was a missense mutation • Hb concentration ≤10.0 g/dL regardless of gender	
	No more than 4 transfusions in the 52-week period prior to treatment and no transfusions in the 3-month period prior to treatment	History of a minimum of 6 transfusion episodes in the 52-week period prior to date of informed consent
Exclusion Criteria	Homozygous for the R479H mutation or 2 non-missense mutations, without the presence of another missense mutation, in the *PKLR* gene	
Baseline Patient Characteristics	• Median age: 33 years (range, 18–78 years) • 40% male; 75% White, 10% Asian • Missense/missense *PKLR* gene variant category: 55 (69%) patients • Missense/non-missense *PKLR* gene variant category: 25 (31%) patients • Median baseline Hb: 8.5 mg/dL (range, 6.4–10.2 g/dL) • History of splenectomy: 73%	• Median age: 36 years (range, 18–68 years) • 26% male; 74% White, 11% Asian • Missense/missense *PKLR* gene variant category: 20 (74%) patients • Missense/non-missense *PKLR* gene variant category: 7 (26%) patients • Median baseline HB: 9.1 g/dL (range, 7.4–10.9 g/dL) • Median of 7 RBC units transfused (range, 3–20 units) standardized to 24 weeks prior to treatment • History of splenectomy: 78%
Associated PKD Complications/ Comorbidities	• Use of iron chelation therapy: 19% • Decrease in BMD: 80% • History of cholecystectomy: 73%	• Use of iron chelation therapy: 89% • Decrease in BMD: 74% • History of cholecystectomy: 85%
Interventions	Patients were randomized 1:1 to: • Pyrukynd (n = 40) up to 50 mg BID for 12 weeks following a 12-week dose titration phase[a] or • Placebo (n = 40)	Patients were administered 50 mg BID for 24 weeks following a 16-week dose titration phase[a]

Table 1. ACTIVATE (NCT03548220) and ACTIVATE-T (NCT03559699) Clinical Trial Description

	ACTIVATE (N = 80)	ACTIVATE-T (N = 27)

Endpoints	**Primary endpoint:** Percentage of participants achieving a HR[b] **Key secondary endpoints:** • Change from baseline in Hb concentration at Weeks 16, 20, and 24 • Change from baseline in bilirubin at Weeks 16, 20, and 24 • Change from baseline in LDH at Weeks 16, 20, and 24 • Change from baseline in reticulocyte percentages at Weeks 16, 20, and 24 • Change from baseline in haptoglobin at Weeks 16, 20, and 24	**Primary endpoint:** Percentage of participants achieving a reduction in transfusion burden[c] **Key secondary endpoint:** Percentage of patients who were transfusion-free

Table 2. ACTIVATE Clinical Trial Results

Endpoint	Pyrukynd (n = 40)	Placebo (n = 40)	Difference[a,b] *P* value
Hemoglobin response, n (%)	16 (40%)	0	39 (24, 55) <0.0001
Hemoglobin (g/dL) Baseline mean (SD) LS mean change (95% CI)	8.6 (1.0) 1.7 (1.3, 2.1)	8.5 (0.8) −0.1 (−0.6, 0.3)	1.8 (1.2 to 2.4) <0.0001
Indirect bilirubin (mg/dL) Baseline mean (SD) LS mean change (95% CI)	4.8 (3.6) −1.2 (−1.7, −0.7)	5.2 (3.6) 0.3 (−0.2, 0.8)	−1.5 (−2.2, −0.9) <0.0001
Reticulocyte (fraction of 1) Baseline mean (SD) LS mean change (95% CI)	0.37 (0.24) −0.10 (−0.13, −0.07)	0.40 (0.22) 0 (−0.02, 0.03)	0.10 (−0.14, 0.06) <0.0001
LDH (U/L) Baseline mean (SD) LS mean change (95% CI)	348 (276) −92 (−124, −60)	260 (140) −21 (−53, 11)	−71 (−116, −26) 0.003
Haptoglobin (mg/dL) Baseline mean (SD) LS mean change (95% CI)	8.2 (10.7) 16.9 (8.8, 25.1)	8.3 (13.8) 1.2 (−7.0, 9.4)	15.8 (4.3, 27.3) 0.008

Abbreviations: CI, confidence interval; Hb, hemoglobin; LDH, lactate dehydrogenase; LS mean change, least square mean change from baseline; SD, standard deviation

In the ACTIVATE trial, serious adverse reactions occurred in 10% of patients receiving Pyrukynd, including atrial fibrillation, gastroenteritis, rib fracture, and musculoskeletal pain that occurred in 1 patient each. The most

common adverse reactions, including laboratory abnormalities, in the ACTIVATE trial were decreased estrone and estradiol in men (56% and 12%, respectively), increased urate (15%), back pain (15%), arthralgia (10%), hypertriglyceridemia, gastroenteritis, hot flush, oropharyngeal pain (8% each), hypertension, arrhythmia, breast discomfort, constipation, dry mouth, and paresthesia (5% each). All rates were higher than placebo.

Hormonal changes in men persisted throughout the study period and returned to close to the baseline levels 28 days after discontinuing Pyrukynd. The adverse reactions reported in the ACTIVATE-T trial were consistent with those seen in ACTIVATE. Acute hemolysis followed by anemia was observed following abrupt discontinuation of Pyrukynd in a doseranging trial. Pyrukynd should be tapered to discontinue treatment if possible.

Safety

ADVERSE EVENTS

The most common adverse reactions including laboratory abnormalities (≥ 10%) in patients with PK deficiency were estrone decreased (males), increased urate, back pain, estradiol decreased (males), and arthralgia.

WARNINGS & PRECAUTIONS

Acute Hemolysis: Avoid abrupt interruption or abrupt discontinuation of Pyrukynd® to minimize the risk of acute hemolysis. A gradual reduction in dosing rather than abrupt cessation is recommended when possible.

CONTRAINDICATIONS

None reported.

Clinical Pharmacology

MECHANISMS OF ACTION

Mitapivat is a pyruvate kinase activator that acts by allosterically binding to the pyruvate kinase tetramer and increasing pyruvate kinase (PK) activity. The red blood cell (RBC) form of pyruvate kinase (PK-R) is mutated in PK deficiency, which leads to reduced adenosine triphosphate (ATP), shortened RBC lifespan, and chronic hemolysis.

Dose & Administration

ADULTS

The starting dosage is 5 mg orally twice daily. To gradually increase hemoglobin, titrate from 5 mg twice daily to 20 mg twice daily, and then to the maximum recommended dose of 50 mg twice daily, with these dose increases occurring every 4 weeks. Assess Hb and transfusion requirement before increasing to the next dose level, as some patients may reach and maintain normal Hb at 5 mg twice daily or 20 mg twice daily. Discontinue if no benefit has been observed by 24 weeks, based on the hemoglobin and hemolysis laboratory results and transfusion requirements.

Table 3: Dose Titration Schedule

Duration	Dosage
Week 1 through Week 4	5 mg twice daily
Week 5 through Week 8	If Hb is below normal range or patient has required a transfusion within the last 8 weeks: • Increase to 20 mg twice daily and maintain for 4 weeks. If Hb is within normal range and patient has not required a transfusion within the last 8 weeks: • Maintain 5 mg twice daily.
Week 9 through Week 12	If Hb is below normal range or patient has required a transfusion within the last 8 weeks: • Increase to 50 mg twice daily and maintain thereafter. If Hb is within normal range and patient has not required a transfusion within the last 8 weeks: • Maintain current dose (5 mg twice daily or 20 mg twice daily).
Maintenance	If Hb decreases, consider up-titration to the maximum of 50 mg twice daily as per the above schedule.

PEDIATRICS

None

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

N/A

HEPATIC IMPAIRMENT

Avoid use in patients with moderate or severe hepatic impairment.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

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