Pharmacy Policy Bulletin: J-1198 Pyrukynd (mitapivat) – Commercial and Healthcare Reform	
Number: J-1198	**Category:** Prior Authorization
Line(s) of Business: ☒ Commercial ☒ Healthcare Reform ☐ Medicare	**Benefit(s):** **Commercial:** **Prior Authorization (1.):** **1.** Miscellaneous Specialty Drugs Oral = Yes w/ Prior Authorization **Quantity Limits (1., 2., 3., or 4.):** **1.** Rx Mgmt Quantity Limits = Safety/Specialty **2.** Rx Mgmt Quantity Limits = Safety/Specialty + Dose Opt **3.** Rx Mgmt Quantity Limits = Safety/Specialty + Dose Opt + Watchful **4.** Quantity Limits = QPC = Yes **Healthcare Reform:** Not Applicable
Region(s): ☒ All ☐ Delaware ☐ New York ☐ Pennsylvania ☐ West Virginia	**Additional Restriction(s):** Not applicable
Version: J-1198-004	**Original Date:** 04/06/2022
Effective Date: 04/25/2025	**Review Date:** 04/09/2025

Drugs Product(s):	• Pyrukynd (mitapivat)
FDA-Approved Indication(s):	• Treatment of hemolytic anemia in adults with pyruvate kinase deficiency (PKD).

Background:	• Pyrukynd is a pyruvate kinase (PK) activator that increases activity of normal and mutated PK enzymes through allosteric binding to the PK tetramer. This increases the hemoglobin (Hb) levels of adults with PKD. • PKD is a rare, genetic blood disorder characterized by low levels of an enzyme called pyruvate kinase (PK) found in the liver and red blood cells (RBCs). Low levels of PK cause chronic hemolysis. PKD is caused by a mutation in the pyruvate kinase liver and red blood cell (*PKLR*) gene and is inherited in an autosomal recessive fashion. • Hemolytic anemia associated with PKD has been historically managed primarily with RBC transfusions, folic acid supplementation, iron chelation therapy, and splenectomy. • In the ACTIVATE clinical trial, patients were included if they had a Hb level ≤ 10 g/dL, and considered not regularly transfused (e.g., ≤ 4 transfusion episodes in

	the previous 12 months). In the ACTIVATE-T trial, patients were included if they had a minimum of 6 transfusions in the previous 52 weeks. • In clinical trials, patients who were homozygous for the R479H variant or had two non-missense variants (without the presence of another missense variant) in the *PKLR* gene were excluded because they did not achieve Hb response in the dose-ranging study. • In the ACTIVATE and ACTIVATE-T trials, patients received concomitant daily folic acid therapy throughout the duration of the study. • Prescribing Considerations: o Pyrukynd should be discontinued if no benefit has been observed by 24 weeks, based on the hemoglobin and hemolysis laboratory results and transfusion requirements. o Pyrukynd has a warning and precaution for acute hemolysis in patients who abruptly interrupt or abruptly discontinue treatment. o Pyrukynd has a warning and precaution for hepatocellular injury. Liver tests should be obtained prior to initiation of Pyrukynd, monthly thereafter for the first 6 months, and as clinically indicated. Pyrukynd therapy should be held if patient experiences clinically significant increases in liver tests or alanine aminotransferase > 5 times the upperlimit of normal. Pryukynd should be discontinued if hepatic injury due to Pyrukynd is suspected. o Avoid use of Pyrukynd in patients with moderate or severe hepatic impairment. o Co-administration with strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, clarithromycin) and inducers (e.g., carbamazepine, phenytoin, rifampin) should be avoided. o Co-administration of moderate CYP3A inhibitors (e.g., erythromycin, fluconazole, verapamil) should be monitored for increased risk of adverse reactions. Do not titrate Pyrukynd beyond 20 mg twice daily. o Co-administration of moderate CYP3A inducers (e.g., phenobarbital, primidone, efavirenz) should be monitored for reduced efficacy of Pyrukynd. If necessary Pyrukynd can be titrated to a maximum recommended dose of 100 mg twice daily.

Approval Criteria

I. Initial Authorization

When a benefit, coverage of Pyrukynd may be approved when all of the following criteria are met **(A. through F.)**:

A. The member is 18 years of age or older.

B. The member has a diagnosis of PKD with hemolytic anemia (ICD-10: D55.21).

C. The provider submits documentation that the member has at least two (2) mutant alleles in the *PKLR* gene, of which at least one (1) is a missense mutation.

D. The provider submits documentation that the member meets all of the following **(1. and 2)**:

1. The member is not homozygous for the R479H mutation.

2. The member does not have two (2) non-missense variants, without the presence of another missense variant in the *PKLR* gene.

E. The member meets one (1) of the following **(1. or 2.)**:

1. There is clinical documentation that the member's hemoglobin level is ≤ 10 g/dL.

2. The member has required at least 6 transfusions in the previous year.

F. The member is receiving concomitant treatment with folic acid.

II. Reauthorization

When a benefit, reauthorization of Pyrukynd may be approved when the following criteria are met **(A. and B.)**:

A. The prescriber attests that the member has experienced a therapeutic response defined as one (1) of the following **(1. or 2.)**:
   1. Hemoglobin increase of ≥ 1.5 g/dL from baseline
   2. Decrease in transfusion burden from baseline

B. The member will continue to receive concomitant treatment with folic acid.

III. Quantity Level Limits

A. Pyrukynd 50 mg Oral Tablets
Coding of the quantity level limitation is at 2 tablets per day. When prior authorization is approved, Pyrukynd 50 mg oral tablets may be authorized in quantities as follows when all of the following criteria are met **(1. and 2.)**:
   1. The member is taking Pyrukynd concomitantly with a moderate CYP3A inducer.
   2. The request is for four (4) tablets per day of Pyrukynd 50 mg oral tablets.

IV. An exception to some or all of the criteria above may be granted for select members and/or circumstances based on state and/or federal regulations

Limitations of Coverage

I. Use of Pyrukynd in moderate to severe hepatic impairment should be avoided.
II. Coverage of drug(s) addressed in this policy for disease states outside of the FDA-approved indications should be denied based on the lack of clinical data to support effectiveness and safety in other conditions unless otherwise noted in the approval criteria.
III. For Commercial or HCR members with a closed formulary, a non-formulary product will only be approved if the member meets the criteria for a formulary exception in addition to the criteria outlined within this policy.

Authorization Duration

Initial Authorization

- Commercial and HCR Plans: If approved, up to a 24 week authorization may be granted.

Reauthorization

- Commercial and HCR Plans: If approved, up to a 12 month authorization may be granted.

Automatic Approval Criteria

None

References:

1. Pyrukynd [package insert]. Cambridge, MA: Agios Pharmaceuticals Inc; January 2025.
2. U.S. Food & Drug Administration. FDA approves treatment for anemia in adults with rare inherited disorder. Available at: https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-treatment-anemia-adults-rare-inherited-disorder#:~:text=FDA%20has%20approved%20Pyrukynd%20(mitapivat,pyruvate%20kinase%20(PK)%20deficiency.. Accessed February 5, 2025.
3. Genetic and Rare Diseases Information Center. Pyruvate kinase deficiency. Available at: https://rarediseases.info.nih.gov/diseases/7514/pyruvate-kinase-deficiency. Accessed February 5, 2025.

4. Secrest MH, Storm M, Carrington, C, et al. Prevalence of pyruvate kinase deficiency: a systematic literature review. Eur J Haematol. 2020;105(2):173-184.
5. Grace RF, Barcellini W. Management of pyruvate kinase deficiency in children and adults. Blood. 2020;136(11):1241-1249.