Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCHEM032.1224	**HEMATOLOGICAL AGENTS** **PYRUKYND®** (mitapivat tablet)
Effective Date: 2/1/2025	**Review/Revised Date**: 10/22, 10/23, 11/24 (TVNT)
Original Effective Date: 08/22	**P&T Committee Meeting Date**: 06/22, 12/22, 12/23, 12/24
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

REQUIRED MEDICAL INFORMATION:
For initiation of therapy, the following criteria must be met:

1. Diagnosis of pyruvate kinase deficiency (PKD). Must include documentation supporting diagnosis (such as chart notes and labs), such as:
    a. Markers of chronic hemolytic anemia (such as low hemoglobin, low haptoglobin, elevated bilirubin, and elevated reticulocytes) and evidence of family history of PKD **OR**
    b. Pyruvate kinase enzyme activity below the lower limit of normal per the laboratory standard (actual laboratory results must be included) **OR**
    c. At least two mutant alleles in the *PKLR* gene
2. Documentation of one of the following:
    a. Hemoglobin less than or equal to 10 mg/dL taken within the previous three months
    b. Patient has had as six or more red blood cell transfusions in the last twelve months

For patients established on therapy, one of the following criteria must be met (Note: Medications obtained as samples, coupons, or any other method of obtaining medications outside of an established health plan benefit are NOT considered established on therapy):

1. Sustained increase in hemoglobin (Hb) of at least 1.5 mg/dL from pre-treatment level. Note: initial hemoglobin level prior to treatment plus a recent level (within the last three months) must be provided **OR**
2. Documentation of a reduction in transfusion burden in the previous 6 months, compared with prior to treatment

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS:
May be approved for patients aged 18 years and older

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a hematologist

COVERAGE DURATION:
Initial authorization will be approved for six months. Reauthorization will be approved for one year.

QUANTITY LIMIT:
56 tablets per 28 days

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION[1]:
Mitapivat (Pyrukynd®) is a pyruvate kinase activator indicated for the treatment of hemolytic anemia in adults with pyruvate kinase deficiency (PKD). Mitapivat is the first and only FDA-approved treatment for pyruvate kinase deficiency induced hemolytic anemia. It activates pyruvate kinase (PK) by binding to the PK tetramer,

resulting in increased PK enzyme activity. It is an oral tablet taken twice daily and titrated according to hemoglobin response.

FDA APPROVED INDICATIONS[1]:
Treatment of hemolytic anemia in adults with pyruvate kinase deficiency

POSITION STATEMENT:
Pyruvate kinase deficiency (PKD) is a rare congenital autosomal recessive disorder caused by variants in the *PKLR* gene, resulting in abnormal or deficient pyruvate kinase (PK) enzyme activity, and ultimately inadequate adenosine triphosphate (ATP), shortened red blood cell lifespan, and chronic hemolysis[7]. Complications related to chronic hemolytic anemia can be mild to severe and include iron overload, infections, bone fractures, bilirubin gallstones, extramedullary hematopoiesis, pulmonary hypertension, liver cirrhosis, and thrombosis[5]. Severe cases can be life-threatening in infancy, and symptoms may also worsen during an infection or in pregnancy. PKD is estimated to be prevalent in 3 to 8 per million people[7], with a higher prevalence in Caucasians (1 per 20,000)[5]. This frequency may be an underestimate due to the challenges in diagnosis and broad spectrum of clinical symptoms. Current treatment options are supportive and include red blood cell transfusions, splenectomy, folic acid supplementation, and chelation due to iron overload[5].

FDA approval for mitapivat was based on two phase three clinical trials, ACTIVATE and ACTIVATE-T. Both trials enrolled patients 18 years of age and older with PKD and at least two mutant alleles in the PKLR gene (of which at least one was a missense mutation), and with a hemoglobin (Hb) concentration less than or equal to 10.0 g/dL. Patients were excluded from the studies if they were homozygous for the R479H mutation or had two non-missense mutations (without the presence of another missense mutation) in the PKLR gene, if they had a splenectomy in the preceding year, or a history of any prior hematopoietic stem cell transplant.

- ACTIVATE was a 26-week randomized, placebo-controlled, double-blind study. Eighty patients were randomized to receive mitapivat up to 50 mg twice daily (after titration) or placebo. The primary endpoint was the percentage of participants achieving a hemoglobin response (HR), defined as at least 1.5 g/dL increase in hemoglobin from baseline sustained at two or more scheduled assessments during the fixed dose period (week 16, 20, or 24 of the study) without transfusions. Hemoglobin, indirect bilirubin, reticulocyte, lactate dehydrogenase, haptoglobin, and daily symptoms were also monitored.
- ACTIVATE-T was a 42-week single-arm, open-label study. Twenty-seven patients with a minimum of 6 transfusion episodes (but no more than 18) in

the 52-week prior were administered mitapivat 50 mg twice daily for 24 weeks (after titration). The primary endpoint was the percentage of participants achieving a reduction in transfusion burden, defined as at least a 33% reduction in transfusion requirements during the 24-week fixed dose period as compared with the subject's historical burden standardized to 24 weeks. The number of patients who were transfusion-free was also evaluated.

Both studies met their endpoints, demonstrating an improvement in hemoglobin and other markers of hemolysis compared to placebo, and a clinically significant decrease in transfusion burden.

ACTIVATE Clinical Trial Results[2]

Endpoint	mitapivat (n = 40)	placebo (n = 40)	Difference *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
Lactate dehydrogenase (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

- The Pyruvate Kinase Deficiency Diary (PKDD) was used to monitor daily symptom score by patients. The LS mean change from baseline with mitapivat 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), in which lower scores represent less sign/symptom severity. The statistical and clinical significance of these results is not clear.

ACTIVATE-T Clinical Trial Results[3]

Endpoint	PYRUKYND N=27

Patients with Transfusion Reduction Response n (%) 95% CI	 9 (33) (17, 54)
Patients who were Transfusion Free n (%) 95% CI	 6 (22) (9, 42)

The most common adverse reactions (at least 5%) were decreased estrone and estradiol in men, increased urate, back pain, arthralgia, hypertriglyceridemia, gastroenteritis, hot flush, oropharyngeal pain, hypertension, arrhythmia, breast discomfort, constipation, dry mouth, paresthesia.

In ACTIVATE, serious adverse events occurred in four patients (10%) receiving mitapivat and two patients (5.1%) in the placebo group. The mitapivat group included atrial fibrillation, gastroenteritis, rib fracture, and musculoskeletal pain and the placebo group included metapneumovirus infection and obstructive pancreatitis. In ACTIVATE-T, serious adverse events occurred in 3 patients (11.1%), including ovarian cyst, renal colic, and increased blood triglycerides. All resolved without dose modification of the treatment except for the patient who experienced serious musculoskeletal pain.

Acute hemolysis with subsequent anemia occurred during trials following abrupt interruption or discontinuation, therefore a gradual taper is recommended. Use of mitapivat should be avoided with strong CYP3A4 inhibitors/inducers; dose reduction may be necessary with moderate CYP3A4 inhibitors/inducers. Mitapivat should be avoided in patients with moderate or severe hepatic impairment

REFERENCE/RESOURCES:

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4. Food and Drug Administration. Integrated Review: PYRUKYND (mitapivat) (2022 Feb). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/216196Orig1s000IntegratedR.pdf (accessed 2022 April 13).
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