Mitapivat (PYRUKYND) in adults with hemolytic anemia due to pyruvate kinase deficiency
National Drug Mini-monograph
DEC 2023

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA APPROVAL INFORMATION

Description / MOA	Mitapivat is an allostatic activator of pyruvate kinase (PK) which increased the activity of the PK enzyme increasing the lifespan of the red blood cell (RBC)[1]
Indication Under Review[i]	Hemolytic anemia due to Pyruvate Kinase (PK) deficiency
Dosage Regimen	Mitapivat starting dose is 5mg twice daily for weeks 1-4, titrated to 20mg twice daily if insufficient increase in hemoglobin, further titrated to max dose of 50 mg twice daily if hemoglobin is not increased and transfusion requirements are not reduced. Abrupt cessation of mitapivat is not recommended and dose taper packs are available from manufacturer to facilitate gradual cessation of treatment
Dosage Forms Under Review	Mitapivat 5mg, 20mg, and 50mg oral tablets

EFFICACY CONSIDERATIONS

Trial	**ACTIVATE**[2]
Design	Randomized, double-blind, placebo-controlled trial
Population	Trial enrolled 80 adult patients who had not had a splenectomy in prior 12 months, no prior bone marrow/stem cell transplantation, and not transfusion dependent at time of enrollment (i.e. last transfusion > 3 months prior). Patients homozygous for PKLR mutation or with only non-missense mutations in PKLR gene were excluded as phase 2 trials demonstrated lack of benefit without at least 1 missense mutant variant of the PKLR gene.[3]
Intervention	Mitapivat or matching placebo 5mg, 20mg or 50mg twice daily for with dose optimization during the first 12 weeks followed by dose maintenance for second 12 weeks. Primary endpoint was increase in Hgb of at least 1.5 g/d for 2 consecutive assessments during week 16, 20, or 24. Secondary endpoints included average change in baseline Hgb, markers of hemolysis, reticulocyte count and two patient-related outcome measures
Results	Sixteen of 40 patients in the mitapivat arm had an increase in Hgb of 1.5g/dL or greater compared to none of the placebo treated patients. All secondary endpoints, including an average increase in Hgb of 1.7 g/dL, favored mitapivat over placebo at a statistically significant level.
Trial	**ACTIVATE-T**
Design	Open label, single arm, phase 3 trial
Population	Twenty-seven patients with laboratory confirmed PK deficiency receiving regular transfusions. Patients without at least 1 missense variant of the PKLR gene were excluded.
Intervention	Mitapivat 5mg, 20mg or 50mg titrated during a 16 week dose optimization and a 24 week fixed dose period. Primary endpoint was 33% reduction in number of RBC units transfused during the 24-week fixed dose period. Secondary endpoints included annualized total number of RBC units transfused, number of transfusion episodes, percent of patients achieving transfusion free status, percent of patients having at least 1 Hgb measurement in normal range during fixed dose period, and changes in laboratory marker of hemolysis.
Results	Ten of 27 patients achieved primary endpoint of a 33% reduction in transfusion burden. For secondary endpoints, transfusion events decreased an average of 1.6 events per24 weeks and transfused units decreased by 2.1 units per 24 weeks. On post-hoc analysis, 6 of the 10 treatment responsive patients were transfusion free for the 24-week fixed dose period.

SAFETY CONSIDERATIONS		
	Boxed Warnings	None
	Contraindications	None
	Other Warnings	Avoid abrupt discontinuation of PYRUKYND to minimize the risk of acute hemolysis. A gradual reduction in dosing rather than abrupt cessation is recommended when possible
	Top 5 AEs	Back Pain (15%), Arthralgia (10%), Hypertriglyceridemia (8%), Gastroenteritis (8%) and hot flush (8%)
	Drug Interactions	Avoid concomitant use with strong CYP3A4 inhibitors or inducers. Dose adjustment of mitapivat is recommended if co-administration with moderate CYP3A inducer or inhibitor cannot be avoided. Mitapivat is an inducer of CYP3A, CYP2B6/2C8/2C9/2C19 enzymes. Monitor for loss of therapeutic effect of drugs metabolized by these enzymes.

SUMMARY / PLACE IN THERAPY	
	Treatment of symptomatic anemia due to PK deficiency is supportive in nature (e.g. transfusions, splenectomy). No other drug therapies are approved for treatment of congenital hemolytic anemia due to PK deficiency. In clinical trials to date, mitapivat has been shown to increase Hgb levels and reduce transfusion requirements in adult patients with at least one missense variant of the PKLR mutation. PK deficiency is a rare condition and use within VA setting expected to be very infrequent. PADR request for mitapivat (all time since approval) include 1 request.

VHA PLACE IN THERAPY		
	Potential Use in VHA	1. As above, rare genetic condition. Use in VHA setting expected to be rare.

REFERENCES:

1.) PYRUKYND Prescribing Information prescribinginfo.pdf (agios.com) Accessed December 2023
2.) Al-Samkari H, et al., Mitapivat versus Placebo for Pyruvate Kinase Deficiency. N Engl J Med. 2022 Apr 14;386(15):1432-1442.
3.) Grace RF, Rose C, Layton DM, et al., Safety and efficacy of mitapivat in pyruvate kinase deficiency. N Engl J Med 2019;381: 933-44.
4.) Glenthøj A, et al.,. Mitapivat in adult patients with pyruvate kinase deficiency receiving regular transfusions (ACTIVATE-T): a multicentre, open-label, single-arm, phase 3 trial. Lancet Haematol. 2022 Oct;9(10):e724-e732.

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