PDL DRUG REVIEW

Proprietary Name: Pyrukynd®
Common Name: mitapivat
PDL Category: Pyruvate Kinase Activators

Summary

Pharmacology/Usage: Mitapivat, the active ingredient of Pyrukynd®, 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.

Indication: For the treatment of hemolytic anemia in adults with pyruvate kinase (PK) deficiency.

There is no pregnancy category for this medication; however, the risk summary indicates that available data from clinical trials are not sufficient to assess for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Untreated PK deficiency in pregnant women may precipitate acute hemolysis, pre-term labor, miscarriage, and severe anemia requiring frequent transfusion. In addition, pre-eclampsia and severe hypertension have been reported. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Film-Coated Tablets: 5mg, 20mg, 50mg. Swallow tablets whole; do not split, crush, chew, or dissolve.

Recommended Dosage: The starting dose is 5mg PO BID, with or without food. To gradually increase hemoglobin (Hb), titrate Pyrukynd® from 5mg BID to 20mg BID, and then to the maximum recommended dose of 50mg BID, 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 5mg BID or 20mg BID. Discontinue Pyrukynd® if no benefit has been observed by 24 weeks, based on hemoglobin and hemolysis laboratory results and transfusion requirements. Refer to the prescribing information for additional information regarding dose titration schedule based on Hb level.

If a dose of Pyrukynd® is missed by 4 hours or less, administer the dose as soon as possible. If a dose is missed by more than 4 hours, do not administer a replacement dose, and wait until the next scheduled dose. Subsequently, return to the normal dosing schedule.

To reduce the risk of acute hemolysis, avoid abrupt interruption or abrupt discontinuation of Pyrukynd® when possible. Taper the dose to gradually discontinue the medication. Monitor patients for signs of acute hemolysis and worsening of anemia. Refer to the prescribing information for additional information regarding a dose taper schedule.

If a dose reduction is required because of an adverse reaction or tolerability, or for a Hb above normal, the dose may be reduced to the next lower dose level, 20mg BID or 5mg BID. If a patient needs to discontinue Pyrukynd®, the dose taper schedule should be followed. In situations where the risk to the patient due to the adverse reaction or Hb

above normal is greater than the risk of acute hemolysis due to sudden withdrawal of the drug, treatment may be discontinued without taper and patients should be monitored for signs of acute hemolysis.

Mitapivat undergoes extensive hepatic metabolism. Moderate and severe hepatic impairment is expected to increase the systemic exposure of mitapivat. Avoid use of Pyrukynd® in patients with moderate and severe hepatic impairment.

Drug Interactions: Avoid the co-administration of strong CYP3A inhibitors with Pyrukynd®.

The co-administration of Pyrukynd® with moderate CYP3A inhibitors will increase mitapivat plasma concentrations; thus, monitor Hb and for increased risks of adverse reactions with Pyrukynd®. Do not titrate Pyrukynd® beyond 20mg BID.

Avoid the co-administration of strong CYP3A inducers with Pyrukynd®.

The co-administration of Pyrukynd® with moderate CYP3A inducers will decrease mitapivat plasma levels; thus, consider alternative therapies that are not moderate CYP3A inducers during treatment with Pyrukynd®. If there are no alternative therapies, monitor Hb and titrate beyond 50mg BID, if necessary, but do not exceed a maximum recommended dose of 100mg BID.

Pyrukynd® induces CYP3A. Thus, monitor patients for loss of therapeutic effect of sensitive CYP3A substrates with narrow therapeutic index when co-administered with Pyrukynd®.

Advise patients using hormonal contraceptives to use an alternative non-hormonal contraceptive method or add a barrier method of contraception during treatment with Pyrukynd®.

Pyrukynd® induces CYP2B6, CYP2C8, CYP2C9, and CYP2C19 enzymes and may decrease systemic concentrations of drugs that are sensitive substrates of these enzymes. Monitor patients for loss of therapeutic effect of sensitive substrates of these enzymes with narrow therapeutic index when co-administered with Pyrukynd®.

Monitor patients for loss of therapeutic effect of UGT1A1 substrates with narrow therapeutic index when co-administered with Pyrukynd®.

Monitor patients for adverse reactions of P-gp substrates with narrow therapeutic index when co-administered with Pyrukynd®.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Pyrukynd®) minus reported % incidence for placebo for all grades. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included back pain (7%), arthralgia (5%), hypertriglyceridemia (5%), gastroenteritis (8%), hot flush (8%), oropharyngeal pain (3%), hypertension (5%), arrhythmia (5%), breast discomfort (5%), constipation (5%), dry mouth (5%), and paresthesia (5%).

Acute hemolysis with subsequent anemia has been observed following abrupt interruption or discontinuation of Pyrukynd® in a dose-ranging study. Avoid abruptly discontinuing Pyrukynd®. Gradually taper the dose of Pyrukynd® to discontinue treatment if possible. When discontinuing treatment, monitor patients for signs of acute hemolysis and anemia, including jaundice, scleral icterus, dark urine, dizziness, confusion, fatigue, or shortness of breath.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Agios Pharmaceuticals, Inc.

Analysis: The efficacy of Pyrukynd® was assessed in a multinational, randomized, double-blind, placebo-controlled study (ACTIVATE) that included adults with PK deficiency (N=80) who were not regularly transfused, defined as

having had no more than 4 transfusions in the 52-week period prior to treatment and no transfusions 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 ≤10g/dL. Patients who were homozygous for the c.1436G>A variant or had 2 non-missense variants (without the presence of another missense variant) in the PKLR gene were excluded. Of the patients with PK deficiency, 40 were randomized to Pyrukynd®. After a period of dose titration up to 50mg BID, patients continued a fixed dose of Pyrukynd® for 12 weeks. There were 88% of patients who were maintained on 50mg BID.

The median duration of treatment with Pyrukynd® was 24.1 weeks. Of the randomized patients, the median age was 33 years (range 18 to 78) and 40% were male. Race was reported in 88% of patients, with 75% being white. The median baseline hemoglobin was 8.5g/dL. Complications and comorbidities associated with PK deficiency included iron overload with a median baseline ferritin of 479ng/ml, chelation therapy use in the year before the first dose of study treatment in 15 patients (19%), decreased bone mineral density in 64 patients (80%) who had a baseline femoral neck T-score or lumbar spine T-score <-1.0, and a history of cholecystectomy in 58 patients (73%).

Efficacy was based upon Hb response, defined as a ≥1.5g/dL increase in Hb from baseline sustained at 2 or more scheduled assessments (weeks 16, 20, and 24) during the fixed dose period without transfusion. The efficacy results, including changes in markers of hemolysis, are in the table below, which was adapted from the prescribing information. All results are statistically significant.

	Pyrukynd® (N=40)	Placebo (N=40)	Difference; p-value
Hb Response, n (%)	16 (40%)	0	39%; <0.0001
Hemoglobin (g/dL)			
Baseline, Mean	8.6	8.5	
LS Mean Change	1.7	-0.1	1.8; <0.0001
Indirect Bilirubin (mg/dL)			
Baseline, Mean	4.8	5.2	
LS Mean Change	-1.2	0.3	-1.5; <0.0001
Reticulocyte (fraction of 1)			
Baseline, Mean	0.37	0.40	
LS Mean Change	-0.10	0	-0.10; <0.0001
Lactate Dehydrogenase (LDH; U/L)			
Baseline, Mean	348	260	
LS Mean Change	-92	-21	-71; 0.003
Haptoglobin (mg/dL)			
Baseline, Mean	8.2	8.3	
LS Mean Change	16.9	1.2	15.8; 0.008

In this study, the least square (LS) mean change from baseline with Pyrukynd® compared to placebo was -0.4 for jaundice (scale of 0-4), -1.1 for tiredness (scare 0-10), and -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.

Most of the Pyrukynd®-treated patients experienced an increase in Hb, while a 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.

In this study, 15 of the 16 patients with a Hb response continued in a long-term extension study and were evaluable for maintenance of response. Thirteen maintained increases in Hb concentration from baseline above the response threshold of ≥1.5g/dL at the last available Hb assessment without requiring any transfusions. The median duration of response for the 16 patients with Hb response was 6.9 months.

The efficacy of Pyrukynd® was assessed in a multinational, single-arm clinical trial (ACTIVATE-T) that included adults with PK deficiency who were regularly transfused (N=27), and 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 c.1436G>A variant or had 2 non-missense variants (without the presence of another missense variant) in the PKLR gene were excluded. Following a period of dose titration up to 50mg BID, patients continued on a fixed dose of Pyrukynd® for 24 weeks.

The median duration of treatment with Pyrukynd® was 40.3 weeks. The median age of included adults was 36 years (range 18 to 68) and 26% were male. Race was reported in 85% of patients, of which 74% were white. The median baseline hemoglobin was 9.1g/dL. Patients had a median of 9 transfusion episodes in the 52 weeks before the first dose of study treatment and a median of 7 red blood cell units transfused standardized to 24 weeks. Patients had evidence of complications and comorbidities associated with PK deficiency including iron overload (median baseline ferritin was 1324ug/L), chelation therapy use in the year before the first dose of study treatment in 24 patients (89%), decreased bone mineral density in 20 patients (74%) who had a baseline femoral neck T-score or lumbar spine T-score <-1.0, and a history of cholecystectomy in 23 patients (85%).

Efficacy was based upon transfusion reduction response and was defined as ≥33% reduction in the number of red blood cell units transfused during the fixed dose period compared with the patient's historical transfusion burden. Efficacy results for patients with PK deficiency who were regularly transfused are presented in the table below, which was adapted from the prescribing information.

	Pyrukynd® (N=27)
Patients with transfusion reduction response	
n (%)	9 (33%)
Patients who were transfusion free	
n (%)	6 (22%)

All 6 patients (22%) who were transfusion free in this study remained transfusion free in a long-term extension study. The median duration of response for the 6 patients was 17 months.

Place in Therapy: Pyrukynd®, an oral pyruvate kinase activator, is indicated for the treatment of hemolytic anemia in adults with pyruvate kinase (PK) deficiency. Pyrukynd® should be avoided in adults with moderate or severe hepatic impairment, and potential drug interactions needs to be assessed. One small study assessed the efficacy of Pyrukynd® as compared with placebo in patients with PK deficiency not regularly transfused. Efficacy was based upon Hb response, and statistically significantly more subjects in the Pyrukynd® group had a Hb response as compared with placebo (NNT 3, calculated by CHC). A second small study assessed the efficacy of Pyrukynd® in

patients with PK deficiency who were regularly transfused. Efficacy was based on transfusion reduction response and 33% of study subjects met this primary endpoint. In addition, 22% were transfusion free. One noted reference source noted that "…it would be reasonable to try mitapivat in any individual with PK deficiency who requires transfusion." Furthermore, it is noted that "mitapivat may also be reasonable in individuals with symptomatic anemia who do not require transfusions, and even in individuals with compensated hemolysis who do not have overt anemia…". Overall the authors suggest mitapivat for adults with PK deficiency with symptomatic anemia (transfusion-dependent or not requiring transfusions).[2]

It is recommended that Pyrukynd® should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Pyrukynd [package insert]. Cambridge, MA: Agios Pharmaceuticals, Inc; 2022.
[2] UpToDate online. Pyruvate kinase deficiency. Accessed June 2022.