CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216196Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	216196
PDUFA Goal Date	February 17, 2022
OSE RCM #	2021-1228
Reviewer Name(s)	Brian Caruth, Pharm.D., BCPS
Associate Director for REMS Design and Evaluation	Laura Zendel, Pharm.D., BCPS
Review Completion Date	February 10, 2022
Subject	Evaluation of Need for a REMS
Established Name	Mitapivat
Trade Name	Pyrukynd
Name of Applicant	Agios Pharmaceuticals, Inc (Agios)
Therapeutic Class	Pyruvate Kinase Activator
Formulation(s)	Oral Tablet
Dosing Regimen	5 mg to 50 mg orally twice daily according to hemoglobin levels assessed every 4 weeks

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Pyrukynd (mitapivat) is necessary to ensure the benefits outweigh its risks. Agios Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 216196 for mitapivat with the proposed indication for the treatment of anemia in adults with pyruvate kinase (PK) deficiency. Mitapivat is associated with an increased risk for acute hemolysis following abrupt interruption or discontinuation. The Applicant did not submit a proposed REMS or risk management plan with this application.

The Division of Risk Management (DRM) has determined that a REMS is not needed to ensure the benefits of mitapivat outweigh its risks. The increased risk for acute hemolysis is similar to the clinical features of patients diagnosed with PK deficiency. Mitapivat is likely to be prescribed in an outpatient setting by genetic specialists familiar with PK deficiency. Prescribers are expected to screen patients for signs and symptoms of acute hemolysis and optimize therapy accordingly. The safety profile of mitapivat, consistent with predicted risks, will be communicated in the Warnings and Precautions section in labeling as well as dose tapering instructions in the dosing and administration section of labeling. At the time of this review, labeling was not final, therefore additional changes could occur.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Pyrukynd (mitapivat) is necessary to ensure the benefits outweigh its risks. Agios Pharmaceuticals, Inc submitted a New Drug Application (NDA) 216196 for mitapivat with the proposed indication for the treatment of anemia in adults with pyruvate kinase (PK) deficiency. This application is under review in the Division of Nonmalignant Hematology (DNH). The Applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Mitapivat, a new molecular entity[a], is a first-in-class pyruvate kinase activator proposed for the treatment of anemia in adults with pyruvate kinase (PK) deficiency. The red blood cell-specific form of pyruvate kinase (PKR) catalyzes the final and irreversible step in glycolysis, converting phosphoenolpyruvate (PEP) to pyruvate, with concomitant formation of the energy carrier molecule adenosine triphosphate (ATP). Mitapivat binds to PKR increasing PK activity in PK-deficient patients.

Mitapivat is proposed to be available as 5 mg, 20 mg, and 50 mg oral tablets. The recommended starting dose is 5 mg twice daily. Dose escalation every 4 weeks is determined using hemoglobin (Hb) levels and transfusion requirements. Table 1 lists the recommended dose adjustments for mitapivat therapy and Table 2 lists the dose taper schedule. Duration of treatment with mitapivat is expected to be long term and likely administered in an outpatient setting.[b] Mitapivat is not currently approved in any jurisdiction.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*
[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

Table 1: Continuation of Treatment and Dose Adjustment for Mitapivat

Duration	Mitapivat Dose Titration	
Day 1 - Week 4	5 mg twice daily	
Assess Hb level every 4 weeks	**If Hb is below normal range or patient has required a transfusion within the last 8 weeks**	**If Hb is within normal range or patient has required a transfusion within the last 8 weeks**
Week 5 - Week 8	Increase to 20 mg twice daily and maintain for 4 weeks	Maintain 5 mg twice daily
Week 9 - Week 12	Increase to 50 mg twice daily and maintain	Maintain current dose (5 mg twice daily or 20 mg twice daily)
Maintenance	If Hb level decreases, consider up-titration to the maximum of 50 mg twice daily as per the above schedule.	

Table 2: Dose Taper Schedule for Mitapivat

Current Dose	Mitapivat Dose Taper Schedule		
	Day 1 – 7	Day 8 – 14	Day 15
5 mg twice daily	5 mg once daily	Discontinue	-
20 mg twice daily	20 mg once daily	5 mg once daily	Discontinue
50 mg twice daily	50 mg once daily	20 mg once daily	

2.2 Regulatory History

The following is a summary of the regulatory history for NDA 216196 relevant to this review:

- 03/24/2015: FDA granted Orphan Drug designation for the treatment of PK deficiency.
- 03/27/2017: IND 119825 submitted with Fast Track designation request.
- 04/27/2017: FDA granted Fast Track designation for the treatment of PK deficiency.
- 06/17/2021: NDA 216196 received for mitapivat.
- 10/05/2021: Mid-Cycle meeting held via teleconference and FDA informed the Applicant that no safety issues that may require a REMS for mitapivat have been identified.
- 12/14/2021: Late-Cycle meeting held via teleconference. FDA informed the Applicant that no safety issues that may require a REMS for mitapivat have been identified.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Pyruvate kinase (PK) deficiency is a rare congenital, autosomal recessive red blood cell glycolysis disorder due to compound heterozygous or homozygous mutations in the pyruvate kinase liver and red blood cell (*PKLR*) gene. Most PK-deficient patients are compound heterozygous for two different missense mutations, rather than homozygous for one mutation. Different tetrameric forms of pyruvate kinase in compound heterozygous individuals result in distinct structural and kinetic properties and limited predictive value of disease severity.[1] PK deficiency results in decreased red blood cell survival,

ineffective erythropoiesis, and lifelong hemolytic anemia.[c] Signs and symptoms of PK deficiency include fatigue, shortness of breath, bone pain, splenomegaly, and jaundice. Gallstones, pulmonary hypertension, extramedullary hematopoiesis, and regular blood transfusions to maintain adequate hemoglobin levels, potentially leading to iron overload, are serious complications associated with PK deficiency.[2] The prevalence is estimated at 51 cases per 1,000,000 in Western populations.[3,d]

3.2 Description of Current Treatment Options

There are no current FDA-approved pharmacologic therapies for PK deficiency. Current supportive therapies for chronic hemolytic anemia due to PK deficiency may include blood transfusions and splenectomy. Splenectomy may reduce the need for regular blood transfusions, although asplenia is associated with an increased risk for sepsis and venous thromboembolism (VTE). Iron chelation therapy may be used for patients at risk of iron overload from frequent blood transfusions. Limited predictive value of disease severity according to mutations in the *PKLR* gene, complications from supportive therapies, and lack of pharmacologic therapies to further improve treatment of PK deficiency represent an unmet medical need.

4 Benefit Assessment

The efficacy of mitapivat for the treatment of adults with PK deficiency was evaluated in two phase 3 studies (Study 006 [NCT03548220] and Study 007 [NCT03559699]). The two studies represented a total of 107 subjects, of whom 40 were randomized to treatment with mitapivat, from approximately 53 sites in 16 countries. All subjects were ≥ 18 years of age and had at least 2 variant alleles in the *PKLR* gene, including at least 1 missense variant. Subjects with a splenectomy scheduled during the study treatment period or having undergone a splenectomy within the previous 12 months were excluded from the studies. Both studies evaluated a 5 mg, 20 mg or 50 mg dose administered orally twice daily. Study 006 was a 26-week, randomized, double-blind, placebo-controlled study in subjects not regularly receiving blood transfusions. Study 007 was a 42-week, open-label study in subjects regularly receiving blood transfusions. Table 3 summarizes the studies 006 and 007.

Table 3: Summary of Studies Contributing to the Primary Efficacy Data of Mitapivat

Study	Study Design	Duration and Dose Evaluated	Subjects	Primary Endpoint	p-value
Phase 3 Studies					
Study 006	Randomized, double-blind, placebo-controlled	26 weeks 2-week taper 5, 20, 50 mg, or placebo	Total: n = 80 40 (mitapivat) 40 (placebo)	increase in Hb ≥ 1.5 g/dL	< 0.0001
Study 007	open-label	42 weeks 3-week taper 5, 20, or 50 mg	Total: n = 27	decrease of ≥ 33% in units of blood transfused	0.0002

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

One subject discontinued treatment in study 006 (1.2%) and seven subjects discontinued treatment in study 007 (25.9%). Baseline demographics in the two studies were generally representative of the target patient population of patients with PK deficiency.

The primary endpoint in Study 006, an increase in hemoglobin of ≥ 1.5 g/dL from baseline, was achieved in 16 subjects (40%) in the mitapivat group compared to no subjects in the placebo group. All pre-specified hierarchical secondary endpoints (change from baseline in the hemolysis parameters of lactate dehydrogenase, indirect bilirubin, haptoglobin, and reticulocytes) and subject reported outcomes (Pyruvate Kinase Deficiency Diary [PKDD] and Pyruvate Deficiency Impact Assessment [PKDIA]) in Study 006 were met. The review team determined the subjects' baseline values from the PKDIA (mitapivat [49.2] and placebo [48.5]) and mean difference between the groups (mitapivat [-4.65] and placebo [-1.39]) were too small to be considered clinically meaningful because the assessment could be impacted by factors other than exclusively mitapivat therapy.

The primary endpoint in Study 007, a decrease of ≥ 33% in the number of blood transfusions compared with the historical transfusion burden, was achieved in 10 subjects (37%) with six of these subjects (22.2%) becoming transfusion free during the study.

The clinical reviewer concluded that substantial evidence of effectiveness supported the benefit of mitapivat. This determination relied on the statistically significant and clinically meaningful results of Study 006 despite excluding results from the PKDIA and clinically significant reduction in transfusion burden in Study 007.

5 Risk Assessment & Safe-Use Conditions

The primary safety review of mitapivat relies on data from four studies (Study 003, Study 006, Study 007, and Study 011) that evaluated mitapivat in subjects with PK deficiency. Study 011 was an extension study of Study 006 and Study 003 was a phase 2, open-label, dose ranging study that evaluated a mitapivat dose of 50 mg twice daily or 300 mg twice daily in 52 subjects. The safety database represents 155 subjects who received at least one dose of mitapivat. The pooled safety set included 67 subjects from Study 006 and Study 007. The safety profile assessment of mitapivat is adequate given the estimated disease prevalence and the inclusion of a double-blind, placebo-controlled study (Study 006).

The most common adverse events in Study 006 (incidence ≥ 10% and occurring more frequently than in the placebo arm) include back pain (15% [6/40]) and arthralgia (10% [4/40]). The incidence of insomnia (17.5% [7/40]) was similar to placebo, however mitapivat appears to be a weak aromatase inhibitor and insomnia has been associated with aromatase inhibitors. Aromatase inhibition also decreases conversion of androstenedione to estrone and testosterone to estradiol. Decreased estrone (56.3% [9/16]) and estradiol (12.5% [2/16]) levels, were observed in male subjects during treatment with mitapivat and were reversible upon discontinuation.

No deaths or TEAEs leading to discontinuation of therapy were reported, however a majority of subjects (92.5% [65/67]) experienced a TEAE with mitapivat therapy. The clinical reviewer focused on acute hemolysis with abrupt interruption or discontinuation of mitapivat therapy.

5.1 ACUTE HEMOLYSIS

Two subjects (3.8%) experienced acute hemolysis in Study 003 after sudden withdrawal of mitapivat. Citing concern that hemoglobin levels would exceed the upper limit of normal (ULN), both subjects discontinued mitapivat without dose tapering. One subject experienced serious Grade 3 acute hemolysis (transfusion or medical intervention indicated) and Grade 3 hemolytic anemia (hemoglobin < 8 g/dL; transfusion indicated). The other subject experienced Grade 2 hemolysis (evidence of hemolysis and greater than or equal to a two gram decrease in hemoglobin). The Applicant implemented a dose taper schedule in Study 006 to address the risk of acute hemolysis observed in Study 003. However, no subjects with a hemoglobin response withdrew from Study 006 and no analysis of acute hemolysis after sudden withdrawal of mitapivat was performed.

Hemolysis is a common clinical feature associated with PK deficiency.[e] The clinical review team agreed with the Applicant's proposal to address the risk of acute hemolysis in the Warnings and Precaution section of the label and include a dose taper schedule in the Dosage and Administration section of the label. Labeling also includes recommendations for monitoring patients for signs of acute hemolysis and anemia including jaundice, scleral icterus, dark urine, dizziness, confusion, fatigue, or shortness of breath when tapering to discontinue treatment.

5.2 REDUCTION IN BONE MINERAL DENSITY

Two fractures (3%) occurred in the pooled safety set in subjects with osteoporosis who received mitapivat. PK deficiency may cause fractures and aromatase inhibitors are known to reduce bone mineral density and increase the risk of fractures. The clinical reviewer considered including a reduction in bone mineral density in the Warnings and Precautions section of the label. Due to insufficient data at this time, the risk will be communicated in the Adverse Reactions section of the label. In addition, the long-term safety of mitapivat will be addressed with two postmarketing requirements evaluating adverse events caused by long-term aromatase inhibition including reduction in bone mineral density.

The clinical reviewer concluded the safety profile of mitapivat is favorable in adults with PK deficiency and the overall benefit-risk profile appears acceptable.

6 Expected Postmarket Use

Mitapivat is likely to be prescribed in an outpatient setting by genetic specialists familiar with PK deficiency. Prescribers are expected to screen patients for signs and symptoms of acute hemolysis and optimize therapy accordingly.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for mitapivat beyond routine pharmacovigilance and labeling.

[e] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

8 Discussion of Need for a REMS

The clinical reviewer recommends approval of mitapivat citing the efficacy and safety data from the two phase 3 studies (Study 006 and Study 007), the seriousness of PK deficiency, and an adequately favorable benefit-risk profile.

The following statutory factors were considering in determining if a REMS was necessary for the benefits of mitapivat to outweigh its risks: the estimated size of the population likely to use the drug, the seriousness of the disease or condition that is to be treated, the expected benefit of the drug, expected or actual duration of treatment, the seriousness of any known or potential adverse events that may be related to mitapivat and the background incidence of such events in the population likely to use the drug and if the drug is a new molecular entity.

PK deficiency is a rare congenital, autosomal recessive red blood cell glycolysis disorder due to compound heterozygous or homozygous mutations in the *PKLR* gene. PK deficiency results in decreased red blood cell survival, ineffective erythropoiesis, and lifelong hemolytic anemia. Gallstones, pulmonary hypertension, extramedullary hematopoiesis, and regular blood transfusions to maintain adequate hemoglobin levels, potentially leading to iron overload, are serious complications associated with PK deficiency.

Two phase 3 studies (Study 006 and Study 007) evaluated efficacy of mitapivat in patients with PK deficiency. Study 006 evaluated subjects not regularly receiving blood transfusions and achieved a statistically significant and clinically meaningful result in the primary endpoint, an increase in hemoglobin of ≥ 1.5 g/dL from baseline, in the mitapivat group compared to placebo. Study 007 demonstrated a clinically significant reduction in transfusion burden with six subjects (22.2%) becoming transfusion free during the study.

The serious risk associated with mitapivat is an increased risk for acute hemolysis following abrupt interruption or discontinuation. In general, healthcare providers who treat PK deficiency should be familiar with monitoring and treating acute hemolysis . Information regarding these risks and appropriate monitoring and tapering will be included in the Warnings and Precautions as well as dosing and administration sections of the labeling. The clinical review team also stated that the safety data do not indicate need for a specific REMS to mitigate the risks for mitapivat and that overall, it has a favorable safety profile. Therefore, this reviewer is not recommending a REMS for the management of the risks of mitapivat therapy.

9 Conclusion & Recommendations

Relying on the data available, a REMS is not necessary to ensure the benefits of mitapivat outweigh the risk for acute hemolysis following abrupt interruption or discontinuation. Information about this risk will be communicated in labeling using the Warnings and Precautions section as well as dose tapering recommendations. In general, we expect healthcare providers who treat patients with PK deficiency are familiar with monitoring and treating the risk of acute hemolysis. At the time of this review, labeling is still under negotiation and the clinical review is ongoing. Should DNH have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10 Appendices

10.1 REFERENCES

[1] van Wijk, R, 2021, Erythrocyte Enzyme Disorders. In: K Kaushansky, MA Lichtman, and JT Prchal, editors, Williams Hematology, 10th edition, New York (NY): McGraw-Hill, 721-811.

[2] Grace RF, C Rose, DM Layton, F Galactéros, W Barcellini, DH Morton, EJ van Beers, H Yaish, Y Ravindranath, KHM Kuo, S Sheth, JL Kwiatkowski, AJ Barbier, S Bodie, B Silver, L Hua, C Kung, P Hawkins, MH Jouvin, C Bowden, and B Glader, 2019, Safety and Efficacy of Mitapivat in Pyruvate Kinase Deficiency, NEJM, 381(10):933-944.

[3] Beutler E, T Gelbart, 2000, Estimating the prevalence of pyruvate kinase deficiency from the gene frequency in the general white population, Blood, 95(11):3585-3588.

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