

Mitapivat: A Quinolone Sulfonamide to Manage Hemolytic Anemia in Adults With Pyruvate Kinase Deficiency

Josef Wills, BA, PharmD, RPh,¹ Melissa Horenstein, BA, PharmD, RPh,²
Alicia Kim, PharmD, RPh,¹ Matthew A. Silva, PharmD, RPh, BCPS,³
and Lorena Dima, MD, PhD^{4*}

Background: Pyruvate kinase (PK) deficiency is a rare enzyme-linked glycolytic defect resulting in mild-to-severe chronic persistent erythrocyte hemolysis. The disease is an autosomal recessive trait caused by mutations in the PK liver and red blood cell gene characterized by insufficient erythrocyte PK activity. PK deficiency is most diagnosed in persons of northern European descent and managed with packed red blood cell transfusions, chelation, and splenectomy with cholecystectomy. Mitapivat is the first approved therapy indicated for hemolytic anemia in adults with PK deficiency with the potential for delaying splenectomy in mild-moderate disease.

Mechanism of Action, Pharmacodynamics, and Pharmacokinetics: Mitapivat is a PK activator that acts by allosterically binding to the PK tetramer and increases PK activity. The red blood cell form of PK is mutated in PK deficiency, which leads to reduced adenosine triphosphate, shortened red blood cell lifespan, and chronic hemolysis. The half-life of elimination is 3–5 hours, with 73% bioavailability, 98% plasma protein binding, and a median duration of response of 7 months.

Clinical Trials: Mitapivat has been investigated through various clinical trials for different therapeutic indications. Pivotal trials that serve the primary focus throughout this article are ACTIVATE, ACTIVATE-T, and RISE. ACTIVATE is a phase 3, randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of mitapivat in adult patients who were not receiving regular blood transfusions. Contrarily, ACTIVATE-T explored the safety and efficacy of mitapivat in adults with PK deficiency who received regular blood transfusions. Both trials demonstrated favorable use of mitapivat in PK deficiency. Focusing on another indication, the ongoing RISE trial investigates the optimal dosage of mitapivat in sickle cell disease.

Therapeutic Advance: Mitapivat is an appropriate treatment for adults with PK deficiency requiring transfusions and may be considered for patients with symptomatic anemia who do not require transfusions and/or PK deficiency with compensated hemolysis without overt anemia.

Keywords: hemolytic anemia, hereditary spherocytosis, mitapivat, pyruvate kinase activator, pyruvate kinase deficiency, sickle cell disease, thalassemia

¹Global Scientific Communications Rare Blood Disorders, Sanofi, Cambridge, MA; ²Gastroenterology, Dupilumab, Sanofi, Cambridge, MA;

³Massachusetts College of Pharmacy and Health Sciences, School of Pharmacy, Worcester, MA; ⁴Transilvania University, Faculty of Medicine, Department of Fundamental Disciplines and Clinical Prevention, Brasov, Romania.

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*Address for correspondence: Professor Lorena Dima, MD, PhD, Faculty of Medicine, Department of Fundamental Disciplines and Clinical Prevention, 56 Nicolae Bălcescu Str., 500019, Brasov, Romania. E-mail: lorena.dima@unitbv.ro

BACKGROUND

Pyruvate kinase (PK) deficiency is a rare enzyme-linked glycolytic defect resulting in mild-to-severe chronic persistent erythrocyte hemolysis with weakness, fatigue, tachycardia, shortness of breath, pallor, and dyspnea.¹ Other clinical indicators of PK deficiency are jaundice, splenomegaly, cholelithiasis, and iron overload from extravascular hemolytic anemia.² The disease is an autosomal recessive trait caused by mutations in the PK liver and red blood cell (PKLR) gene located on chromosome 1q21 characterized by insufficient erythrocyte PK activity. The first pathogenic variants responsible for PK deficiency were identified in 1991 and now >300 different variants and multiple genotype-phenotype correlations are known.³ PK deficiency is most diagnosed in persons of northern European descent and managed with packed red blood cell transfusions, chelation, and splenectomy with cholecystectomy.⁴ Transfusions are individualized and indicated for severe disease with hemolytic anemia. Splenectomy and concomitant cholecystectomy are recommended for individuals requiring frequent blood transfusions for severe hemolytic anemia and are typically laparoscopic or performed concurrently. Mitapivat is the first approved therapy indicated for hemolytic anemia in adults with PK deficiency with the potential for delaying splenectomy in mild-moderate disease and is currently under investigation for beta-thalassemia and sickle cell disease. Coadministration of folic acid is used to avoid folate deficiency.⁵

CHEMICAL DESCRIPTION

Mitapivat sulfate has an extensive chemical structure with a molecular weight of 1053.23 g/mol. Its molecular formula is $(C_{24}H_{26}N_4SO_3)_2 \cdot H_2SO_4 \cdot 3H_2O$ and chemical name is 8-quinolinesulfonamide, N-[4-[[4 (cyclopropylmethyl)-1-piperazinyl]carbonyl]phenyl]-, sulfate, hydrate (2:1:3).⁶ In addition, its IUPAC name is N-[4-[4-(cyclopropylmethyl) piperazine-1-carbonyl]phenyl]quinoline-8-sulfonamide, sulfuric acid, trihydrate. Mitapivat sulfate is a white-to-off-white solid that is slightly soluble in water, available as branded Pyrukynd in 5 mg, 20 mg, and 50 mg tablets for oral administration.⁷ The inactive ingredients are croscarmellose sodium, mannitol, microcrystalline cellulose, sodium stearyl fumarate, FD&C Blue No. 2, hypromellose, lactose monohydrate, titanium dioxide, and triacetin.

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MAIN INDICATION(S)

Mitapivat is currently indicated for the treatment of hemolytic anemia in adults with PK deficiency. It will continue to be investigated in pediatric populations with PK deficiency (ACTIVATE-kids and ACTIVATE-kidsT), adults with thalassemia (Phase 3 trials ENERGIZE and ENERGIZE-T), and adults with sickle cell disease (Phase 2/3 RISE UP study).^{8,9} It has been granted orphan drug status for PK deficiency, thalassemia, and sickle cell disease in the United States and for PK deficiency in Europe.¹⁰

MECHANISM OF ACTION AND PHARMACODYNAMICS

The PK enzyme catalyzes the conversion of phosphoenolpyruvate to pyruvate, the last step of the glycolytic pathway, which results in adenosine triphosphate (ATP) formation. Because erythrocytes lack mitochondria, the production of energy is totally dependent on the anaerobic glycolysis, namely, on the ATP produced through the reaction catalyzed by PK. Therefore, PK enzyme is essential for the survival of mature erythrocytes and for TCA cycle in their precursors.¹¹ The enzyme has 4 isoforms: the red cell and the liver isoforms, encoded by PKLR gene, and muscle-1 and muscle-2 isoforms, encoded by PKM gene.^{11,12} Heterozygous or homozygous mutations in the PKLR gene result in enzyme compounds with either reduced affinity for their substrate (phosphoenolpyruvate) or for the allosteric activator (fructose 1,6-bisphosphate; FBP) or with altered stability of PK tetramers.^{11,13} The red blood cell form of PK is mutated in PK deficiency, which leads to inadequate ATP, shortened red blood cell lifespan, chronic hemolysis, and inefficient hematopoiesis.^{13,14} PKD is the most common cause of congenital nonspherocytic hemolytic anemia.^{13,14} Therapeutic agents that increase ATP production might be useful in a spectrum of hemolytic anemias resulting from deficits of various glycolytic enzymes.¹⁰

Mitapivat is a first-in-class oral small-molecule PK activator that acts by allosterically binding to the PK tetramer and stabilizing the tetramer (the active form of the enzyme). By increasing the affinity for PK substrate phosphoenolpyruvate, mitapivat upregulates erythrocyte PK activity.¹¹ Consequently, it increases ATP production and reduces levels of 2,3-DPG.¹⁰ Because mitapivat uses a different allosteric site from FBP—the physiologic allosteric activator of erythrocyte PK—the drug activates both wild-type and

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mutant enzymes, including those not induced by FBP.^{10,13}

In both animal studies and ex vivo human blood samples, mitapivat enhanced the glycolytic pathway.^{13,15} Ex vivo treatment with mitapivat was shown to enhance PK activity, protein stability, and ATP levels in various PKLR genotypes.¹⁶ In a phase 1 study on healthy volunteers, mitapivat increased in vivo the PK activity and the level of erythrocytes ATP and reduced the upstream glycolytic intermediate, 2,3-diphosphoglycerate (2,3-DPG).¹⁷ In the phase II study on 52 patients with PKD, mitapivat administration increased the hemoglobin level with more than 1 g/dL in more than 50% of subjects, and the response was sustained up to 35 weeks in the 19 patients included in the extension phase of this study. The red cell hemoglobin response was found to be related to the genotype, probability of response being higher in patients with at least 1 missense mutation, and with the protein level of red-cell PK at baseline, suggesting that a minimum level of normal chain PK is a prerequisite for mitapivat activation.^{12,18}

PHARMACOKINETICS AND DRUG INTERACTIONS

The C_{max} at steady state was 101.2, 389.9, and 935.2 ng/mL for 5, 20, and 50 mg twice daily, respectively. Mitapivat T_{max} values at steady state were 0.5-to-1.0-hour postdose across the dose range of 5–50 mg twice daily. The absolute bioavailability after a single dose was approximately 73%. Mitapivat is highly protein-bound at 97.7% plasma with low red blood cell distribution.⁹ Mitapivat undergoes extensive hepatic metabolism, and persons with moderate and severe hepatic impairment (secondary cirrhosis from transfusion-related iron overload) are expected to have increased systemic exposure and may avoid mitapivat. The half-life ranges from 3 to 5 hours after multiple dose administrations of 5 mg twice daily to 20 mg twice daily. The total recovery of a radiolabeled mitapivat after a single oral dose was 89.2%, with 49.6% in the urine and 39.6% in the feces. The clinically significant adverse reaction seen with mitapivat was acute hemolysis with abrupt treatment discontinuation.

In vitro studies demonstrated that mitapivat is primarily metabolized mainly by CYP3A4 but also by CYP1A2, CYP2C8, and CYP2C9.^{17,19,20} Mitapivat has been found to induce CYP3A4 and CYP2B6.¹⁰ The concomitant use of strong inducers or inhibitors of CYP3A4 should be avoided,¹¹ and doses should be limited to 20 mg twice daily in association with moderate inhibitors. Because mitapivat is a substrate and

inhibitor of P-glycoprotein (P-gp) and also induces UGT1A1, association with substrates with narrow therapeutic index of either P-gp or UGT1A1 should be avoided.⁹ Mitapivat is also a mild-to-moderate inhibitor of the aromatase enzyme (CYP19A1), the enzyme involved in biosynthesis of estrogens from androgen precursors, but the clinical implications of these effects on the long-term use of mitapivat have not been established yet.¹⁰

CLINICAL TRIALS

ACTIVATE

ACTIVATE was a phase 3, randomized, double-blind, placebo-controlled study conducted to evaluate the efficacy and safety of mitapivat in 80 adult subjects with PK deficiency who were not regularly transfused. Eligibility criteria of subjects included, but were not limited to, a minimum age of 18 years, the presence of at least 2 variant alleles in the PKLR gene, no transfusions in the 3-month period before treatment, and a hemoglobin less than or equal to 10 g/dL.⁷

Patients in this study were randomized to receive either mitapivat or placebo. This study was designed in 2 parts: (1) A dose escalation period starting at 5 mg of mitapivat or placebo twice daily, up to 20 mg twice daily or 50 mg twice daily over a 12-week period, and (2) a 12-week follow-up period with a fixed dose of mitapivat.²¹ Investigators followed biomarkers of hemolysis and hematopoiesis, such as hemoglobin, indirect bilirubin, haptoglobin, lactate dehydrogenase, and reticulocyte percentages.

The results indicated that 40 percent of patients randomized to mitapivat, compared with 0 patients in the placebo group, achieved a hemoglobin response (defined as a sustained ≥ 1.5 g/dL increase in hemoglobin concentration from baseline) at weeks 16, 20, and 24 during the fixed-dose period.⁸ Treatment with mitapivat proved to be statistically significant in improving key secondary end points, including average change from baseline in hemoglobin, markers of hemolysis, and markers of hematopoietic activity over placebo use. No adverse events occurred that resulted in discontinuation of mitapivat or placebo. Overall, mitapivat proved to be a safe and efficacious molecule while increasing hemoglobin in patients with no infusion history.

ACTIVATE-T

Because mitapivat was effective in adult patients with PK deficiency who were not receiving regular transfusions (ACTIVATE), ACTIVATE-T aimed to evaluate the safety and efficacy of mitapivat in an adult

population receiving regular transfusions. ATIVATE-T was a multicenter, open-label, single-arm, phase 3 trial. Inclusion criteria was similar to that of ACTIVATE; however, ACTIVATE-T included patients receiving regular transfusions (at least 6 episodes in the previous year).

Patients received oral mitapivat during a 16-week dose optimization period (5, 20, and 50 mg twice daily) and a 24-week fixed-dose period. The primary end point was a reduction in transfusion burden ($\geq 33\%$ reduction in the number of RBC units transfused during the fixed-dose period, compared with the participant's individual historical transfusion burden, standardized to 24 weeks).²² Efficacy and safety were assessed in all participants who received at least 1 dose of mitapivat.

In this clinical trial, 27 patients were enrolled and received at least 1 dose of mitapivat. Of those 27 patients, a reduction in transfusion burden by at least 33% was found in 10 participants (37%).⁹ The most common treatment-emergent adverse events were increase in alanine aminotransferase, headache, increase in aspartate aminotransferase, fatigue, and nausea.⁷ Overall, investigators found mitapivat to be pivotal in reducing transfusion burden in some adults with PK deficiency because they received regular transfusion.

RISE UP

The RISE UP trial was a phase 1 study that assessed the use of mitapivat (AG-348) in adult patients with sickle cell disease (SCD). In SCD, hemoglobin S (HbS) polymerization causes red cell sickling, hemolysis, and vaso-occlusion. The rationale of pursuing this study is that the mechanism of mitapivat provides the molecule to potentiate antisickling properties in SCD by increasing glycolytic activity and ATP. Patients who were included in RISE UP were at least 18 years old; had a confirmed diagnosis of sickle cell disease (HbSS genotype); had a baseline hemoglobin of 7 g/dL or greater; and had no recent transfusions, erythropoietin therapy, or changes in SCD-specific therapies including hydroxyurea and L-glutamine. Subjects received either 3 or 4 ascending dose levels of mitapivat twice daily (5, 20, 50, 100 mg) for 2 weeks duration each, followed by a 12–15 days taper.²³ For each dose level, pharmacokinetics, pharmacodynamics, and markers of oxygen affinity and HbS polymerization were assessed at different stages of the study.

The investigator's findings were an increase in Hb at the 50 mg BID dosage (mean 1.2 g/dL), a Hb response (defined as a ≥ 1 g/dL increase in Hb) in half the study population at any dose level compared with baseline, and a constant increase in mean ATP levels.²¹ Patients

also experienced a mean reduction in the hemolytic biomarkers during the dose escalation. It was concluded that mitapivat improved anemia while demonstrating safety and tolerability at multiple dose levels in SCD.

In addition to normalization of hemoglobin, reduction of hemolysis, and of the transfusion burden, data from the abovementioned studies showed that mitapivat also improves ineffective erythropoiesis and decreases iron overload in PK deficient patients.²⁴

SAFETY PROFILE

Despite its effect on aromatases, data from DRIVE-PK,²⁵ ACTIVATE,²¹ ACTIVATE-T,²⁴ and the long-term extension (LTE) study (NCT03853798) proved a favorable safety profile of mitapivat for bone mineral density.²⁶

COST-BENEFIT ANALYSIS

Cost-benefit considerations related to PK deficiency management incorporate multiple recurrent hospitalizations for hemolytic anemia, supportive care, transfusion, and related complications along with procedures and supplementation. Diagnosis is typically difficult, requiring extensive and expensive workup and may evade clinicians and individuals for months to years with persistent symptoms and progressive disease, requiring supportive management with transfusions and limited by transfusion-related complications.⁵

Patients with severe hemolytic anemia from PK deficiency are managed with blood transfusions and/or splenectomy for supportive care; both are associated with costly complications. Blood transfusions result in iron overload from extensive hemolysis and increased iron absorption due to ineffective erythropoiesis. Chelation and phlebotomy can be used to counter manage iron overloaded individuals. Splenectomy carries the risk of sepsis and postsurgical complications with necessary monitoring for procedural-related thrombosis. Preprocedural vaccinations, antimicrobial treatment and prophylaxis, 2 or more days of in-hospital recovery for uncomplicated procedures, and 2–4 weeks of careful postoperative follow-up in outpatient clinic are necessary.²⁷

The mean lifetime direct cost of a patient with PK deficiency is estimated to be \$3.3 million, according to a model compiled by Agios Pharmaceuticals (holding the US patent for mitapivat). Patients with PK deficiency were stratified by age (early pediatrics, adolescents, and adults), and the adult population was

further grouped by transfusion status (regularly transfused, not regularly transfused, and not transfused). The main cost-drivers are the adoption rate and acquisition cost of mitapivat along with that of chelation, recurrent phlebotomy, transfusions, procedures, monitoring, hospitalization, and costs associated with complications.²⁸

A 28-day supply of Pyrukynd is approximately \$28,000 monthly (\$336,000/year) at most retail pharmacies.²⁹ Agios offers a copay program that lowers copay to \$0 for some eligible commercially insured patients and a patient assistance program that offers free prescriptions of Pyrukynd to some eligible uninsured and underinsured patients.⁸ In clinical trials with a clinical response rate of 40%, the monthly acquisition cost is out of reach of many, even when discounted to an adjusted value of \$11,200/month (monthly cost × clinical trial response rate).

Mitapivat is an appropriate treatment for adults with PK deficiency requiring transfusions to reduce treatment burden and may also be appropriate for those with symptomatic anemia who do not require transfusions to reduce the need transfusions and related complications. Mitapivat is also considered for PK deficiency with compensated hemolysis without overt anemia because these patient populations may have mild symptoms that only become apparent when hemolysis is reduced and reduce the risk of iron accumulation because of iron overload. Mitapivat is ineffective in patients who are compound heterozygotes for 2 nonmissense mutations.¹⁶

Most patients in clinical trials to date had low hemoglobin levels, recurrent and necessary transfusions, and high rates of splenectomy and cholecystectomy, indicating a patient population with severe anemia (phase 3 ACTIVATE trial) under careful management. The ENERGIZE trial inclusion criteria included beta- or alpha-thalassemia and need for transfusions while the RISE UP trial is requiring patients with documented disease, 2–10 sickle cell pain crises, and hemoglobin between 5.5 and 10.5 grams. These inclusion criteria suggest that mitapivat may be appropriate for treating patients with severe hemolytic disease from different etiologies.²⁷

THERAPEUTIC ADVANCE

Mitapivat is the first approved disease-modifying therapy for hemolytic anemia in adults with PK deficiency. The ACTIVATE and ACTIVATE-T trials demonstrated efficacy and acceptable safety of mitapivat regardless of transfusion frequency and is currently under review for treating moderate-to-severe sickle cell anemia and

thalassemia. At an estimated adjusted cost of \$11,200/month, mitapivat is not the most cost-effective therapeutic option for PK deficiency but is substantiated by meaningful early clinical indicators of benefit, including reductions in transfusion burden and increases in hemoglobin levels.

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