

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AQVESME safely and effectively. See full prescribing information for AQVESME.

AQVESME™ (mitapivat) tablets, for oral use
Initial U.S. Approval: 2022

WARNING: HEPATOCELLULAR INJURY

See full prescribing information for complete boxed warning.

AQVESME can cause serious hepatocellular injury. Measure liver laboratory tests (ALT, AST, alkaline phosphatase, and total bilirubin with fractionation) at baseline and every 4 weeks for 24 weeks and then as clinically indicated. Avoid use of AQVESME in patients with cirrhosis. Discontinue AQVESME if hepatocellular injury is suspected. (5.1)

AQVESME is available only through a restricted program called the AQVESME REMS. (5.2)

INDICATIONS AND USAGE

AQVESME is a pyruvate kinase activator indicated for the treatment of anemia in adults with alpha- or beta-thalassemia. (1.1)

DOSAGE AND ADMINISTRATION

- The tablet should be swallowed whole. Do not split, crush, chew, or dissolve the tablets. (2.1)
- Recommended dose is 100 mg orally twice daily with or without food. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 100 mg. (3)

CONTRAINDICATIONS

None. (4)

ADVERSE REACTIONS

The most common adverse reactions were headache and insomnia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Agios Pharmaceuticals, Inc. at 1-833-228-8474 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong CYP3A Inhibitors and Inducers: Avoid concomitant use. (7.1)
- Moderate CYP3A Inhibitors: Avoid concomitant use. (7.1)
- Moderate CYP3A Inducers: Consider alternatives that are not moderate inducers. If there are no alternatives, see Full Prescribing Information for recommended dosage for drug interactions with moderate CYP3A inducers. (2.4, 7.1)
- Sensitive CYP3A substrates including hormonal contraceptives: Avoid concomitant use with substrates that have narrow therapeutic index. (7.2)
- CYP2B6, CYP2C and UGT1A1 Substrates: Monitor patients for efficacy of the substrates with narrow therapeutic index. (7.2)
- P-gp Substrates: Monitor patients for adverse reactions of the substrates with narrow therapeutic index. (7.2)

USE IN SPECIFIC POPULATIONS

Hepatic Impairment: Avoid use of AQVESME in patients with cirrhosis (Child-Pugh Class A, B or C). (8.6)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: HEPATOCELLULAR INJURY

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Important Dosage and Administration Information
- 2.2 Recommended Dosage
- 2.3 Monitoring for Safety
- 2.4 Recommended Dosage for Drug Interactions

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Hepatocellular Injury
- 5.2 AQVESME REMS

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience

7 DRUG INTERACTIONS

- 7.1 Effect of Other Drugs on AQVESME
- 7.2 Effect of AQVESME on Other Drugs

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: HEPATOCELLULAR INJURY

AQVESME can cause serious hepatocellular injury. Measure liver laboratory tests (ALT, AST, alkaline phosphatase, and total bilirubin with fractionation) at baseline and every 4 weeks for 24 weeks and then as clinically indicated. Avoid use of AQVESME in patients with cirrhosis. Discontinue AQVESME if hepatic injury is suspected [see Warnings and Precautions (5.1)].

Because of the risk of hepatocellular injury, AQVESME is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the AQVESME REMS [see Warnings and Precautions (5.2)].

1 INDICATIONS AND USAGE

AQVESME is indicated for the treatment of anemia in adults with alpha- or beta-thalassemia.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Information

- AQVESME is taken with or without food.
- Swallow tablets whole. Do not split, crush, chew, or dissolve the tablets.
- If a dose of AQVESME is missed by 4 hours or less, administer the dose as soon as possible. If a dose of AQVESME 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.
- Monitor for hepatocellular injury during treatment with AQVESME [see Dosage and Administration (2.3)].

2.2 Recommended Dosage

The recommended dosage for adults with alpha- or beta-thalassemia is AQVESME 100 mg orally twice daily.

Treatment with AQVESME is intended to be long-term. Discontinue AQVESME if no benefit in hemolytic anemia has been observed, based on the totality of laboratory results and clinical status of the patient, unless there is another explanation for response failure (e.g., bleeding, surgery, other concomitant illnesses).

Interruption or Discontinuation

If a patient needs to interrupt or discontinue AQVESME for any reason, a dose taper is not necessary.

2.3 Monitoring for Safety

Prior to Initiating Treatment with AQVESME

- Check liver tests including ALT, AST, alkaline phosphatase, total bilirubin with fractionation, before first AQVESME dose.

During Treatment with AQVESME

- After the first dose, check liver tests including ALT, AST, alkaline phosphatase, total bilirubin with fractionation every 4 weeks for 24 weeks and as clinically indicated thereafter.

When Drug-Induced Liver Injury Is Suspected

- Interrupt AQVESME and complete a comprehensive evaluation to rule out other causes of liver injury.
- If AQVESME-related liver injury caused new or worsening jaundice or ALT $\geq 10 \times$ baseline, do NOT restart AQVESME.
- If AQVESME-related liver injury is not ruled out, but peak ALT is $< 10 \times$ baseline without elevation of bilirubin above baseline, and if AQVESME is resumed, reinitiate liver test monitoring every 4 weeks for 24 additional weeks.
- If AQVESME-related liver injury is ruled out, AQVESME may be restarted at provider discretion. Resume liver test monitoring schedule that existed prior to stopping AQVESME.

AQVESME Interruption Due to Non-Liver Causes

- If AQVESME was stopped for any reason for ≤ 8 weeks other than suspected AQVESME-related liver injury, resume the liver test monitoring schedule that existed prior to stopping AQVESME.
- If AQVESME was stopped for more than 8 weeks, restart liver test monitoring every 4 weeks for 24 additional weeks upon resumption of treatment with AQVESME.
- If treatment is stopped for any duration after 24 weeks of monitoring and treatment, resume monitoring as clinically indicated.

2.4 Recommended Dosage for Drug Interactions

Moderate CYP3A Inducers

Consider alternative therapies that are not moderate CYP3A inducers during treatment with AQVESME. If there are no alternative therapies, monitor Hb and do not exceed the maximum recommended dose of 100 mg orally twice daily [see *Drug Interactions (7.1)* and *Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

- 100 mg tablets: oblong, blue, film-coated tablets with "M100" printed on both sides.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatocellular Injury

AQVESME can cause hepatocellular injury. Avoid use of AQVESME in patients with cirrhosis. In patients with thalassemia treated with AQVESME, liver injury with and without jaundice has been observed within the first 6 months of exposure. Obtain liver tests (including ALT, AST, alkaline phosphatase, total bilirubin with fractionation) prior to the initiation of AQVESME, then every 4 weeks for the first 24 weeks, and as clinically indicated thereafter. Interrupt AQVESME if clinically

significant increases in liver tests are observed or alanine aminotransferase is >5 times the upper limit of normal (ULN). Complete a comprehensive evaluation to rule out other causes of liver injury when drug-induced liver injury (DILI) is suspected. Discontinue AQVESME if hepatocellular injury due to AQVESME is suspected [*see Dosage and Administration (2.3)*].

Symptoms and signs of early liver injury may mimic those of thalassemia. Advise patients to report new or worsening symptoms of loss of appetite, nausea, right upper quadrant abdominal pain, vomiting, scleral icterus, jaundice, or dark urine while on AQVESME treatment.

During the double-blind period, 2 of 301 patients (0.66%) with thalassemia treated with AQVESME experienced adverse reactions suggestive of hepatocellular injury. Three additional patients experienced adverse reactions suggestive of hepatocellular injury during the open-label extension periods after switching from placebo to AQVESME. Of these 5 patients, two had serious liver injury and were hospitalized including 1 patient who developed jaundice (peak bilirubin 32 mg/dL). Another patient developed jaundice (peak bilirubin 4 mg/dL) without being hospitalized. These reactions were characterized by a time to onset within the first 6 months of treatment with peak elevations of alanine aminotransferase of $>5 \times \text{ULN}$ with or without jaundice. All patients discontinued treatment with AQVESME, and these reactions improved upon treatment discontinuation.

AQVESME is available only through a restricted program under a REMS [*see Warnings and Precautions (5.2)*].

5.2 AQVESME REMS

AQVESME is available only through a restricted program under a REMS called the AQVESME REMS because of the risk of hepatocellular injury.

Notable requirements of the AQVESME REMS include the following:

- Prescribers must be certified by enrolling in the REMS and completing training.
- Prescribers must counsel patients receiving AQVESME about the risk of hepatocellular injury.
- Prescribers must monitor liver tests (including ALT, AST, alkaline phosphatase, total bilirubin with fractionation, and other tests as clinically indicated) to determine if the patient is appropriate to receive AQVESME treatment.
- Patients must enroll in the REMS and comply with the monitoring requirements.
- Pharmacies must be certified by enrolling in the REMS and must only dispense to patients who are authorized to receive AQVESME.

Further information is available at www.aqvesmerems.com or 1-800-625-9951.

6 ADVERSE REACTIONS

The following clinically significant adverse reaction is described elsewhere in labeling:

- Hepatocellular Injury [*see Warnings and Precautions (5.1)*].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Alpha- and Beta-Thalassemia

A total of 301 patients with thalassemia received AQVESME, administered at 100 mg orally twice daily, for up to 59.9 weeks in the ENERGIZE trial (N=129) and the ENERGIZE-T trial (N=172) [see *Clinical Studies (14)*].

ENERGIZE Trial

Patients with non-transfusion-dependent thalassemia received AQVESME (N=129) or placebo (N=63).

The most common adverse reactions ($\geq 5\%$ and at least 5% higher in the AQVESME arm) in patients with non-transfusion-dependent thalassemia were headache and insomnia.

ENERGIZE-T Trial

Patients with transfusion-dependent thalassemia received AQVESME (N=172) or placebo (N=85).

The most common adverse reactions ($\geq 5\%$ and at least 5% higher in the AQVESME arm) in patients with transfusion-dependent thalassemia were headache and insomnia.

Serious adverse reactions occurred in 1.3% of patients with thalassemia treated with AQVESME, including supraventricular arrhythmia and supraventricular tachycardia. Permanent discontinuations of AQVESME due to an adverse reaction occurred in 1.3% of patients and included elevated hepatic transaminases and insomnia.

Table 1 summarizes the adverse reactions in the ENERGIZE and the ENERGIZE-T trials, individually and combined.

Table 1: Adverse Reactions^a in Patients with Alpha- and Beta-Thalassemia Receiving AQVESME

Adverse Reactions	ENERGIZE (Non-transfusion-dependent)		ENERGIZE-T (Transfusion-dependent)		Total	
	AQVESME (N=129)	Placebo (N=63)	AQVESME (N=172)	Placebo (N=85)	AQVESME (N=301)	Placebo (N=148)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Headache	29 (22.5)	6 (9.5)	46 (26.7)	10 (11.8)	75 (24.9)	16 (10.8)
Insomnia ^b	35 (27.1)	5 (7.9)	38 (22.1)	8 (9.4)	73 (24.3)	13 (8.8)

^a Included adverse reactions that occurred in at least 5% of patients in the AQVESME arm and at least 5% higher than the placebo arm.

^b Term includes initial insomnia, middle insomnia, and terminal insomnia.

Variations in Reproductive Hormones

Increases in serum testosterone (T) concentrations and decreases in serum estradiol (E2) concentrations were observed in men receiving AQVESME (Table 2). These changes in hormones were maintained during treatment with AQVESME. In 3 male patients who discontinued AQVESME and in whom reproductive hormone data were available following discontinuation of AQVESME, the hormone changes were reversible. In female patients, sex hormone analysis was limited due to physiologic variations in hormones during the menstrual cycle and the use of hormonal contraceptives.

Table 2: Abnormalities in Reproductive Hormones in Men with Thalassemia Receiving AQVESME

Parameter	ENERGIZE (Non-transfusion-dependent)		ENERGIZE-T (Transfusion-dependent)	
	AQVESME (46 males)	Placebo (25 males)	AQVESME (64 males)	Placebo (31 males)
Reproductive hormone analyses				
Testosterone (T)				
Serum T concentration (mean)				
Baseline	613 ng/dL	505 ng/dL	625 ng/dL	666 ng/dL
Change from baseline	228 ng/dL	-2.8 ng/dL	108 ng/dL	66 ng/dL
Serum T increased ^a				
Baseline	2.2%	4.3%	3.3%	10%
Change from baseline	18.6%	0%	13.5%	6.9%
Estradiol (E2)				
Serum E2 concentration (mean)				
Baseline	29.6 pg/mL	27.3 pg/mL	26.4 pg/mL	28.9 pg/mL
Change from baseline	-8.7 pg/mL	0 pg/mL	-5.0 pg/mL	1.6 pg/mL
Serum E2 decreased ^b				
Baseline	0%	9.5%	10.2%	6.9%
Change from baseline	2.5%	0%	8.5%	3.6%

^a Percentage of subjects with serum T concentration above the upper limit of normal (greater than 1050 ng/dL) at baseline and percentage of subjects with serum T increases from baseline to above the upper limit of normal where baseline was within normal limits.

^b Percentage of subjects with serum E2 concentration below the lower limit of normal at baseline and percentage of subjects with serum E2 decreases from baseline to below the lower limit of normal where baseline was within normal limits.

Note: Results from the ENERGIZE-T study do not include data from patients who received concomitant testosterone replacement therapies.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on AQVESME

Strong CYP3A Inhibitors	
Clinical Impact	- Co-administration of AQVESME with strong CYP3A inhibitors increased mitapivat plasma concentrations [see <i>Clinical Pharmacology (12.3)</i>]. - Increased mitapivat plasma concentrations may increase the risks of adverse reactions of AQVESME.
Prevention or Management	Avoid co-administration of strong CYP3A inhibitors with AQVESME [see <i>Dosage and Administration (2.4)</i>].
Moderate CYP3A Inhibitors	
Clinical Impact	Co-administration of AQVESME with moderate CYP3A inhibitors will increase mitapivat plasma concentrations [see <i>Clinical Pharmacology (12.3)</i>].

Prevention or Management	Avoid co-administration of moderate CYP3A inhibitors with AQVESME [see <i>Dosage and Administration (2.4)</i>].
Strong CYP3A Inducers	
Clinical Impact	- Co-administration of AQVESME with strong CYP3A inducers decreased mitapivat plasma concentrations [see <i>Clinical Pharmacology (12.3)</i>]. - Decreased mitapivat plasma concentrations will reduce the efficacy of AQVESME.
Prevention or Management	Avoid co-administration of strong CYP3A inducers with AQVESME [see <i>Dosage and Administration (2.4)</i>].
Moderate CYP3A Inducers	
Clinical Impact	Co-administration of AQVESME with moderate CYP3A inducers will decrease mitapivat plasma concentrations [see <i>Clinical Pharmacology (12.3)</i>].
Prevention or Management	Consider alternative therapies that are not moderate CYP3A inducers during treatment with AQVESME. If there are no alternative therapies, monitor Hb and do not exceed the maximum recommended dose of 100 mg twice daily [see <i>Dosage and Administration (2.4)</i>].

7.2 Effect of AQVESME on Other Drugs

CYP3A Substrates	
Clinical Impact	AQVESME induces CYP3A. Co-administration of AQVESME will decrease systemic concentrations of drugs that are sensitive CYP3A substrates, including hormonal contraceptives (e.g., ethinyl estradiol) [see <i>Clinical Pharmacology (12.3)</i>].
Prevention or Management	- Avoid co-administration of AQVESME with sensitive CYP3A substrates that have narrow therapeutic index when co-administered with AQVESME. - Avoid concomitant use with hormonal contraceptives except for intrauterine systems containing levonorgestrel. If contraception is desired or needed, use an alternative contraceptive that is not affected by enzyme inducers. If concomitant use is unavoidable, use additional nonhormonal contraception during concomitant use and for 28 days after discontinuation of AQVESME.
CYP2B6 and CYP2C Substrates	
Clinical Impact	AQVESME induces CYP2B6, CYP2C8, CYP2C9, and CYP2C19 enzymes <i>in vitro</i>, and may decrease systemic concentrations of drugs that are sensitive substrates of these enzymes [see <i>Clinical Pharmacology (12.3)</i>].
Prevention or Management	Monitor patients for loss of therapeutic effect of sensitive substrates of these enzymes with narrow therapeutic index when co-administered with AQVESME.

UGT1A1 Substrates	
Clinical Impact	• AQVESME induces UGT1A1 <i>in vitro</i> and may decrease systemic concentrations of drugs that are UGT1A1 substrates [see <i>Clinical Pharmacology (12.3)</i>].
Prevention or Management	• Monitor patients for loss of therapeutic effect of UGT1A1 substrates with narrow therapeutic index when co-administered with AQVESME.
P-gp Substrates	
Clinical Impact	• AQVESME inhibits the P-gp transporter <i>in vitro</i> and may increase systemic concentrations of drugs that are P-gp substrates [see <i>Clinical Pharmacology (12.3)</i>].
Prevention or Management	• Monitor patients for adverse reactions of P-gp substrates with narrow therapeutic index when co-administered with AQVESME.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from clinical trials of AQVESME are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes.

In animal reproduction studies, mitapivat orally administered twice daily to pregnant rats and rabbits during organogenesis was not teratogenic at exposures up to 9.9- and 2.4-fold the human exposure associated with the MRHD, respectively. Mitapivat administered orally to pregnant rats twice daily during organogenesis through lactation did not result in adverse developmental effects at doses up to 9.9 times the MRHD (*see Data*).

The estimated background risk of major birth defects for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal Risk

Transfusion requirements in thalassemia patients are increased during pregnancy. Pregnant women with transfusion-dependent thalassemia are considered high risk, with their major complications being cardiac in origin, including cardiac dysrhythmia, right ventricular dysfunction, and cardiac failure, reported in 1.1% to 15.6%. Pregnant women with non-transfusion-dependent thalassemia need to be monitored and treated for risk of thrombosis, especially those who are splenectomized or infrequently transfused. Patients with non-transfusion-dependent thalassemia may develop a need for regular transfusions during pregnancy, and in such patients the risk of alloimmunization should be carefully evaluated. All pregnant women with thalassemia should be closely monitored for iron overload.

Data

Animal Data

In an embryo-fetal development study in rats, mitapivat was administered at doses of 5, 10, 25, and 100 mg/kg twice daily by oral gavage during the period of organogenesis (gestation days 6 to 17). There was a statistically significant 14% decrease in maternal net body weight gain at 100 mg/kg twice daily with associated decrease in food consumption. Enlarged or fused placenta and/or a distended amniotic sac, an increase in post-implantation loss (early and late resorptions), a decrease in the mean number of viable fetuses, lower mean fetal weights, and fetal external, visceral, and skeletal malformations were observed at 100 mg/kg twice daily, (48 times the MRHD, based on area under the plasma drug concentration-time curve [AUC]). No maternal or embryo-fetal toxicity was observed up to 25 mg/kg twice daily (9.9 times the MRHD, based on AUC).

In an embryo-fetal development study in rabbits, mitapivat was administered at doses of 12.5, 30, and 62.5 mg/kg twice daily by oral gavage during the period of organogenesis (gestation days 7 to 20). Lower fetal weight was observed at 62.5 mg/kg twice daily (2.4 times MRHD, based on AUC) and correlated with reduced maternal body weight gain. No effects on fetal morphology were observed.

In a pre- and post-natal development study in rats, mitapivat was administered at doses of 5, 10, 25, and 100 mg/kg twice daily by oral gavage during the period of organogenesis and continuing to weaning (gestation day 7 to lactation day 20). Dystocia was observed at ≥ 25 mg/kg twice daily (≥ 9.9 times MRHD, based on AUC). At 100 mg/kg twice daily (48 times MRHD, based on AUC) decreased maternal body weight gain, prolonged parturition, and dystocia occurred and resulted in maternal mortality, complete litter loss, decreased pup viability and decreased pup body weight. No adverse effects on pup growth and development, and reproductive performance were observed up to 50 mg/kg (9.9 times the MRHD, based on AUC).

8.2 Lactation

Risk Summary

There are no data on the presence of AQVESME or its metabolites in human or animal milk, the effects on the breastfed child, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AQVESME and any potential adverse effects on the breastfed child from AQVESME or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of AQVESME did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects.

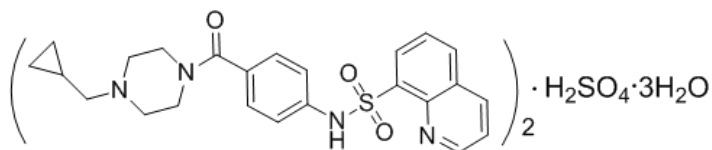
8.6 Hepatic Impairment

Avoid use in patients with cirrhosis (Child-Pugh Class A, B, or C) due to an increased risk of severe outcomes if hepatocellular injury occurs [*see Warnings and Precautions (5.1)*]. In patients with cirrhosis Child-Pugh Class B and C, there is a potential increase in AQVESME exposure [*see Clinical Pharmacology (12.3)*].

11 DESCRIPTION

The active ingredient of AQVESME is mitapivat, a pyruvate kinase activator, present as mitapivat sulfate. The chemical name of mitapivat sulfate is 8-quinolinesulfonamide, N-[4-[[4-

(cyclopropylmethyl)-1-piperazinyl]carbonyl]phenyl]-, sulfate, hydrate (2:1:3). The chemical structure of mitapivat sulfate is:



The molecular formula is $(\text{C}_{24}\text{H}_{26}\text{N}_4\text{SO}_3)_2 \cdot \text{H}_2\text{SO}_4 \cdot 3\text{H}_2\text{O}$, and the molecular weight is 1053.23 for mitapivat sulfate. Mitapivat sulfate is a white to off-white solid and is slightly soluble in water.

AQVESME is available as 100 mg tablets for oral administration. Each tablet contains 100 mg mitapivat free base, provided as 117.0 mg of the sulfate hydrate salt, and the following inactive ingredients: croscarmellose sodium, mannitol, microcrystalline cellulose, and sodium stearyl fumarate.

The 100 mg tablet film coating contains the inactive ingredients FD&C Blue No. 2, hypromellose, lactose monohydrate, titanium dioxide, triacetin, and macrogol/PEG. The tablets are imprinted with blue ink containing the inactive ingredients ammonium hydroxide, FD&C Blue No. 1, isopropyl alcohol, n-butyl alcohol, propylene glycol, shellac glaze, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Mitapivat is a pyruvate kinase activator that acts by allosterically binding to the pyruvate kinase tetramer and increasing pyruvate kinase (PK) activity. Imbalances in globin chain production during erythropoiesis result in increased oxidative stress, which leads to ineffective erythropoiesis and hemolysis. In nonclinical models of beta-thalassemia, mitapivat improved energy homeostasis, RBC longevity, ineffective erythropoiesis, and hemolysis by increasing PK activity.

12.2 Pharmacodynamics

Mitapivat decreases 2,3 diphosphoglycerate (2,3-DPG) and increases ATP in healthy volunteers and in patients with thalassemia.

Cardiac Electrophysiology

At a dose 3 times the recommended dose, mitapivat did not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

The population pharmacokinetic model simulated C_{max} , C_{trough} , AUC_{0-12} and accumulation ratio of mitapivat at the recommended dosage is listed in Table 3.

Table 3: Steady State Mitapivat Exposure at the Recommended Dosage^a

Mitapivat Dosage	C_{max} (ng/mL)	C_{trough} (ng/mL)	AUC_{0-12} (ng*h/mL)	Accumulation Ratio
100 mg twice daily ^b	1641.7 (12.9%)	71 (18.5%)	4835.6 (5.8%)	0.83

^a Pharmacokinetic parameters are presented as geometric mean (CV%). The interval of the last 12 hours was selected for steady state PK parameters calculation. Residual error was not included during simulation.

^b The simulations were performed at steady state.

Absorption

Median t_{max} values at steady state were 0.5 to 1.0 hour post-dose at 100 mg twice daily.

The absolute bioavailability after a single dose was approximately 73%.

Effect of Food

Following administration of a single dose of AQVESME in healthy subjects, a high-fat meal (approximately 900 to 1,000 total calories, with 500 to 600 calories from fat, 250 calories from carbohydrate, and 150 calories from protein) did not change the exposure (AUC_{inf}) of mitapivat, but reduced the rate of mitapivat absorption, with a 42% reduction in C_{max} and a delay in t_{max} of 2.3 hours when compared to dosing under fasted conditions.

Distribution

Mitapivat is highly protein bound (97.7%) in plasma with low RBC distribution (RBC-to-plasma ratio of 0.37). The mean volume of distribution at steady state (V_{ss}) was 42.5 L.

Elimination

Population pharmacokinetics derived median CL/F at steady state was 17.7 L/h at 100 mg twice daily.

Metabolism

In vitro studies showed that mitapivat is primarily metabolized by CYP3A4. Following a single oral dose of 120 mg of radiolabeled mitapivat to healthy subjects, unchanged mitapivat was the major circulating component.

Excretion

After a single oral administration of radiolabeled mitapivat to healthy subjects, the total recovery of administered radioactive dose was 89.2%, with 49.6% in the urine (2.6% unchanged) and 39.6% in the feces (<1% unchanged).

Specific Populations

No clinically meaningful effects on the pharmacokinetics of mitapivat were observed based on age, sex, race, or body weight.

Pediatric Population

The pharmacokinetics of mitapivat in children and adolescents (<18 years old) have not been studied.

Hepatic Impairment

Mitapivat undergoes extensive hepatic metabolism. The pharmacokinetics of mitapivat were studied in adult subjects with moderate hepatic impairment (Child-Pugh Class B). After a single oral administration of 50 mg mitapivat, subjects with moderate hepatic impairment demonstrated 36% greater exposure (AUC_{∞}) to mitapivat, compared to subjects with normal hepatic function. Geometric mean C_{max} values were similar between the groups. There were no major changes to plasma protein binding or elimination half-life in subjects with moderate hepatic impairment relative to healthy controls. The pharmacokinetics of mitapivat in subjects with severe hepatic impairment (Child-Pugh Class C) have not been studied.

Renal Impairment

The effects of renal impairment on mitapivat pharmacokinetics were assessed with population pharmacokinetic analyses. Steady state AUC of mitapivat in patients with eGFR 60 to <90 mL/min/1.73 m² was not significantly different compared to patients with eGFR $\geq$ 90 mL/min/1.73 m². There are limited data available in patients with eGFR 30 to <60 mL/min/1.73 m² and no data available in patients with eGFR <30 mL/min/1.73 m².

Drug Interaction Studies

Clinical Studies and Model-Based Approaches

Effect of Strong CYP3A Inhibitors on AQVESME

Itraconazole (a strong CYP3A inhibitor) increased mitapivat AUC_{inf} and C_{max} by 4.9-fold and 1.7-fold, respectively, following a single AQVESME dose of 20 mg. Itraconazole increased mitapivat AUC_{0-12} and C_{max} by 1.9-fold and 1.6-fold, respectively, following AQVESME 100 mg twice daily.

Ketoconazole (a strong CYP3A inhibitor) increased mitapivat AUC_{0-12} and C_{max} by approximately 3.9-fold and 2.4-fold, respectively, following AQVESME 100 mg twice daily.

Effect of Moderate CYP3A Inhibitors on AQVESME

Fluconazole (a moderate CYP3A inhibitor) increased mitapivat AUC_{0-12} and C_{max} by 2.7-fold and 1.7-fold, respectively, following AQVESME 100 mg twice daily.

Effect of Strong CYP3A Inducers on AQVESME

Rifampin (a strong CYP3A inducer) decreased mitapivat AUC_{inf} and C_{max} by 91% and 77%, respectively, following a single AQVESME dose of 50 mg. Rifampin decreased mitapivat AUC_{0-12} and C_{max} by 93% and 82%, respectively, following AQVESME 100 mg twice daily.

Effect of Moderate CYP3A Inducers on AQVESME

Efavirenz (a moderate CYP3A4 inducer) decreased mitapivat AUC_{0-12} and C_{max} by 52% and 21%, respectively, following AQVESME 100 mg twice daily.

Effect of AQVESME on CYP3A substrates

Midazolam (a CYP3A substrate) AUC_{inf} and C_{max} decreased by 65% and 59%, respectively, with AQVESME 100 mg twice daily.

Effect of AQVESME on P-gp Substrates

Co-administration of AQVESME with drugs that are substrates of P-gp may result in a clinically relevant increase in plasma concentrations of these substrates.

In vitro Studies

CYP450 and UGT Enzymes

Mitapivat induces CYP2B6, CYP2C8, CYP2C9, CYP2C19, and UGT1A1.

Drug Transporter Systems

Mitapivat is a substrate and an inhibitor of P-gp.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Mitapivat was not carcinogenic in transgenic rasH2 mice up to the highest doses tested at 500 mg/kg/day in males and at 250 mg/kg/day in females when given orally for 26 weeks.

Mitapivat was not carcinogenic in rats when given orally up to 300 mg/kg/day in males and 200 mg/kg/day in females, at systemic exposures 35 times and >86 times the MRHD, respectively, based on AUC.

Mutagenesis

Mitapivat was not mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay. Mitapivat was not clastogenic in an *in vitro* human lymphocyte micronucleus assay or in an *in vivo* rat bone marrow micronucleus assay.

Fertility

In a fertility and early embryonic development study, oral administration of mitapivat twice daily in male rats prior to and during mating at doses up to 300 mg/kg/day, which represents 34 times the MRHD of 100 mg twice daily, based on AUC, did not result in adverse effects on fertility or reproductive function. In female rats, twice daily oral administration of mitapivat prior to mating and continuing through organogenesis, at doses up to 200 mg/kg/day, which represents 37 times the MRHD of 100 mg twice daily, based on AUC, did not result in adverse effects on fertility or reproductive function.

14 CLINICAL STUDIES

Patients with Transfusion-Dependent and Non-Transfusion-Dependent alpha- or beta-Thalassemia

Transfusion-Dependent alpha- or beta-Thalassemia

The efficacy of AQVESME was evaluated in ENERGIZE-T, a multinational, randomized, double-blind, placebo-controlled clinical study (NCT04770779) of 258 adult patients with transfusion-dependent alpha- or beta-thalassemia, defined as having had 6 to 20 RBC units transfused and no longer than a 6-week transfusion-free period during the 24 weeks prior to randomization. Patients were included if they had a documented diagnosis of thalassemia (beta-thalassemia with or without alpha-globin gene mutations, HbE/beta-thalassemia, or alpha-thalassemia/HbH disease). Randomization was stratified by geographical region (North America and Europe vs Asia-Pacific vs Rest of World) and thalassemia genotype (β^0/β^0 vs non- β^0/β^0).

Among the 258 patients with transfusion-dependent alpha- or beta-thalassemia, 171 patients were randomized to receive 100 mg of AQVESME twice daily during the 48-week double-blind period.

The median duration of treatment with AQVESME was 48.1 weeks (range: 0.3 to 59.9 weeks). Overall, 104 (60.5%) patients were exposed to AQVESME for >48 weeks. Among the 258 randomized patients, the median age was 33.5 years (range: 18 to 67) and 47.3% were male; 62.0% were from North America and Europe, 18.2% were from Asia-Pacific, and 19.8% were from the rest of the world; race was reported in 95.7% of patients: 60.1% White, 30.2% Asian, 0.8% Black or African American, 0.8% Multiracial, and 3.9% unknown.

The baseline disease characteristics are shown in Table 4.

Table 4: Baseline Disease Characteristics in Patients with Transfusion-Dependent Thalassemia (ENERGIZE-T)

Baseline Disease Characteristics	AQVESME N=171	Placebo N=87	Total N=258
Hemoglobin (g/dL), n^a			
Median	9.0	8.9	8.9
(min, max)	(5.1, 11.8)	(5.1, 10.9)	(5.1, 11.8)
Thalassemia Genotype, n (%)			
beta ⁰ /beta ⁰	75 (44)	39 (45)	114 (44)
non-beta ⁰ /beta ⁰	96 (56)	48 (55)	144 (56)

Baseline Disease Characteristics	AQVESME N=171	Placebo N=87	Total N=258
Transfusion Burden (RBC units), n (%)^b			
≤12	54 (32)	21 (24)	75 (29)
>12	117 (68)	66 (76)	183 (71)
Hepatic Iron Concentration (mg/g), n	133	74	207
Median	4.58	4.43	4.55
(min, max)	(0.37, 28.21)	(0.37, 20.47)	(0.37, 28.21)
Prior History of Splenectomy, n (%)	92 (54)	49 (56)	141 (55)
Prior History of Cholecystectomy, n (%)	42 (25)	24 (28)	66 (26)
Prior History of Iron Chelation, n (%)	165 (96)	87 (100)	252 (98)
Prior History of Hydroxyurea, n (%)	7 (4.1)	3 (3.4)	10 (3.9)

Hb: hemoglobin, RBC: red blood cells

^a Pretransfusion Hb threshold is the mean of all pretransfusion Hb concentrations for the RBC transfusions administered during the 24-week period before randomization.

^b Total number of RBC units transfused in the 24-week period before randomization.

Efficacy was based upon transfusion reduction response, defined as ≥50% reduction in the number of red blood cell units transfused with a reduction of at least 2 units of RBCs transfused in any consecutive 12-week period through Week 48 compared with baseline. The efficacy results are shown in Table 5.

Table 5: Efficacy Results in Patients with Transfusion-Dependent Thalassemia (ENERGIZE-T)

	AQVESME N= 171	Placebo N=87	Difference	
<i>Endpoints</i>	<i>n (%)</i>	<i>n (%)</i>	<i>Adjusted Rate Difference^a (%) (95% CI)</i>	<i>p-value^b</i>
≥50% reduction from baseline in RBC units transfused in any consecutive 12 weeks, with a reduction of at least 2 units	52 (30.4)	11 (12.6)	17.6 (8.0, 27.2)	0.0003
<i>Endpoints</i>	<i>n (%)</i>	<i>n (%)</i>	<i>Adjusted Rate Difference^b (%) (95% CI)</i>	<i>p-value^a</i>
≥50% reduction from baseline in RBC units transfused in any consecutive 24 weeks	23 (13.5)	2 (2.3)	11.1 (5.1, 17.0)	0.0003
≥33% reduction from baseline in RBC units from Week 13 through Week 48	25 (14.6)	1 (1.1)	13.4 (7.7, 19.1)	<0.0001
≥50% reduction from baseline in RBC units from Week 13 through Week 48	13 (7.6)	1 (1.1)	6.4 (1.9, 10.9)	0.0056

CI: confidence interval, RBC: red blood cell

^a All p-values are 2-sided and all results are statistically significant.

^b The difference is adjusted for randomization stratification factors, which included geographical region (North America and Europe vs Asia-Pacific vs Rest of World) and thalassemia genotype (β^0/β^0 vs non- β^0/β^0). The two-sided p-value is based on the Mantel-Haenszel stratum weighted method adjusting for the randomization stratification factors.

Non-Transfusion-Dependent alpha- or beta-Thalassemia

The efficacy of AQVESME was evaluated in ENERGIZE, a multinational, randomized, double-blind, placebo-controlled clinical study (NCT04770753) of 194 adults with non-transfusion-dependent alpha- or beta-thalassemia, defined as having had no more than 5 RBC units transfused during the 24-week period prior to randomization and no RBC transfusions within 8 weeks prior to informed consent and during the screening period. Patients were included if they had a documented diagnosis of thalassemia (beta-thalassemia with or without alpha-globin gene mutations, HbE/beta-thalassemia, or alpha-thalassemia/HbH disease) and a baseline Hb concentration ≤ 10 g/dL. Randomization was stratified by baseline Hb concentrations (≤ 9 g/dL vs 9.1-10 g/dL) and thalassemia genotype (alpha-thalassemia/HbH disease vs beta-thalassemia).

Among the 194 patients with non-transfusion-dependent alpha- or beta-thalassemia, 130 patients were randomized to receive 100 mg of AQVESME twice daily during the 24-week double-blind period.

The median duration of treatment with AQVESME was 24.1 weeks (range: 1.1 to 28.1 weeks). Overall, 97 (75%) patients were exposed to AQVESME for >24 weeks. Among the 194 randomized patients, the median age was 41 years (range: 18 to 69) and 36.6% were male; race was reported in 99% of patients: 56.2% White, 39.2% Asian, 1.0% Black or African American, 0.5% Multiracial, and 2.1% unknown.

The baseline disease characteristics are shown in Table 6.

Table 6: Baseline Disease Characteristics in Patients with Non-Transfusion-Dependent Thalassemia (ENERGIZE)

Baseline Disease Characteristics ^a	AQVESME N=130	Placebo N=64	Total N=194
Hemoglobin (g/dL), n	130	64	194
Median	8.4	8.4	8.4
(min, max)	(5.3, 10.4)	(5.9, 10.7)	(5.3, 10.7)
Thalassemia Genotype, n (%)			
alpha-thalassemia/HbH disease	42 (32)	20 (31)	62 (32)
beta-thalassemia	88 (68)	44 (69)	132 (68)
Transfusion Burden (RBC units)^b, n (%)			
0	114 (87.7)	54 (84.4)	168 (86.6)
1-2	10 (7.7)	7 (10.9)	17 (8.8)
3-5	6 (4.6)	3 (4.7)	9 (4.6)
Reticulocyte (Fraction of 1), n	122	58	180
Median	0.05	0.04	0.05
(min, max)	(0.00, 0.30)	(0.00, 0.22)	(0.00, 0.30)
Indirect Bilirubin (mg/dL), n	130	62	192
Median	1.37	1.32	1.34
(min, max)	(0.13, 9.11)	(0.15, 4.77)	(0.13, 19.11)
LDH (U/L), n	130	64	194
Median	264	267	265
(min, max)	(108, 1208)	(110, 1009)	(108, 1208)

Baseline Disease Characteristics^a	AQVESME N=130	Placebo N=64	Total N=194
Hepatic Iron Concentration (mg/g), n	98	52	150
Median	3.93	2.76	3.64
(min, max)	(0.75, 27.19)	(0.75, 18.53)	(0.75, 27.19)
Prior History of Splenectomy, n (%)	47 (36)	25 (39)	72 (37)
Prior History of Cholecystectomy, n (%)	45 (35)	16 (25)	61 (31)
Prior History of Iron Chelation, n (%)	46 (35)	22 (34)	68 (35)
Prior History of Hydroxyurea, n (%)	11 (8.5)	6 (9.4)	17 (8.8)

Hb: hemoglobin, LDH: lactate dehydrogenase, RBC: red blood cell

^a n is the number of patients with non-missing data.

^b Total number of RBC units transfused in the 24-week period before randomization.

Efficacy was based upon Hb response, defined as a ≥ 1 g/dL increase in average Hb concentration from Week 12 through Week 24 compared with baseline and a mean change from baseline in fatigue-related symptoms and impacts assessed by a patient-reported outcome instrument, the Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue). See Table 7 for efficacy results.

Table 7: Efficacy Results in Patients with Non-Transfusion-Dependent Thalassemia (ENERGIZE)

	AQVESME N= 130	Placebo N=64	Difference	
Endpoint	n (%)	n (%)	Adjusted Rate Difference (%) (95% CI)	p-value^a
Hb Response ^b	55 (42.3)	1 (1.6)	40.9 (32.0, 49.8)	<0.0001
Endpoint	LS mean (95% CI)	LS mean (95% CI)	LS mean difference (95% CI)	p-value^a
Hemoglobin (g/dL) ^c	0.86 (0.73, 0.99)	-0.11 (-0.28, 0.07)	0.96 (0.78, 1.15)	<0.0001
FACIT-Fatigue ^d	4.85 (3.41, 6.30)	1.46 (-0.43, 3.34)	3.40 (1.21, 5.59)	0.0026

CI: confidence interval, Hb: hemoglobin, LS: least squares

^a All p-values are 2-sided and all results are statistically significant.

^b For Hb response, the difference is adjusted for randomization stratification factors, which included Hb concentrations (≤ 9.0 g/dL vs 9.1-10.0 g/dL) and thalassemia genotype (alpha-thalassemia/HbH disease vs beta-thalassemia). The two-sided p-value is based on the Mantel-Haenszel stratum weighted method adjusting for the randomization stratification factors.

^c Change from baseline in average Hb concentration from Week 12 through Week 24.

^d Change from baseline in average FACIT-Fatigue score from Week 12 through Week 24. FACIT-Fatigue total scores range from 0 to 52 with higher scores indicating less fatigue. At baseline, patients reported a mean FACIT-Fatigue score of approximately 36 in both the AQVESME and placebo arms.

Note: For the endpoints of change from baseline in average Hb concentration from Week 12 through Week 24 and change from baseline in average FACIT-Fatigue score from Week 12 through Week 24, the 95% CIs and the two-sided p-values are based on an analysis of covariance (ANCOVA) model, which included change from baseline as the dependent variable, treatment group as the independent variable, and baseline and the randomization stratification factors as covariates. The results are based on observed cases.

Eighty-seven percent of patients in the AQVESME arm experienced an increase from baseline in average Hb from Weeks 12 through 24 (see Figure 1). Figure 2 depicts change from baseline in

hemoglobin over time.

Figure 1: Average Change from Baseline in Hemoglobin from Week 12 through Week 24 by Patient – All Randomized Patients (ENERGIZE)

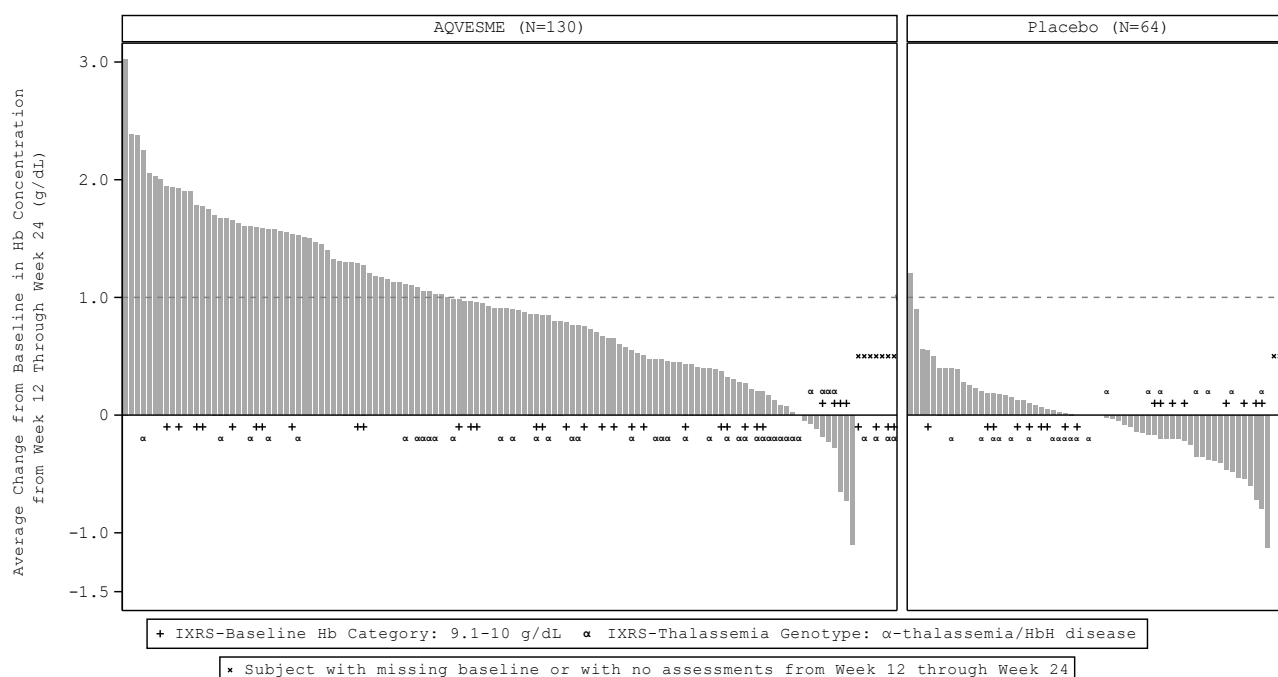
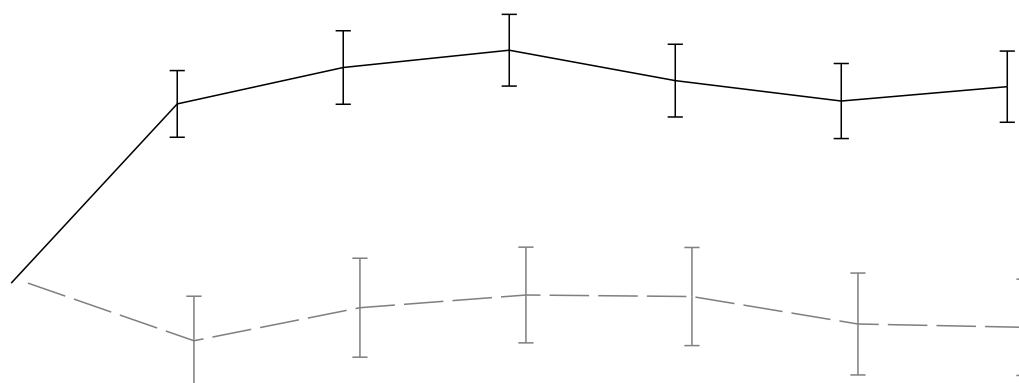


Figure 2: Change from Baseline in Hemoglobin Over Time – All Randomized Patients (ENERGIZE)



Of the 55 patients with Hb response in the AQVESME arm, the average increase in Hb was 1.6 g/dL and the median duration of response was 19.6 weeks (range: 4.0 to 23.4+ weeks) during the 24-week double-blind period.

Patients in the AQVESME arm experienced an improvement compared to placebo in the change from baseline to Week 24 for 2 markers of hemolysis (indirect bilirubin [-0.62 mg/dL (95% CI: -0.80 ,

−0.44)] and lactate dehydrogenase [−24.28 U/L (95% CI: −45.40, −3.15)]).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

AQVESME 28-Day Packs				
Tablet Strength	Package Configuration	Tablet Description	Tablet Imprint	NDC
100 mg	Carton containing 4 blister wallets. Each blister wallet contains 14 tablets.	Oblong, blue, film-coated tablets	"M100" printed on both sides	Carton: 71334-235-00 Blister wallet: 71334-235-14

Storage

Store in a refrigerator 2°C to 8°C (36°F to 46°F).

AQVESME may be stored at room temperature, 20°C to 25°C (68°F to 77°F) for up to 3 months. The discard date is 3 months after removal of the tablets from the refrigerator. Write the discard date in the space provided on the blister wallet and/or the carton. Discard the tablets if not used within 3 months or if the expiration date has passed, whichever occurs first. Dispense and store the blister wallets in the original carton until use.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Hepatocellular Injury

Inform patients of the risk of hepatocellular injury with AQVESME. In patients with thalassemia treated with AQVESME, liver injury has been observed within the first 6 months of treatment. Tell patients to immediately report any new or worsening symptoms suggestive of liver injury including loss of appetite, nausea, right upper quadrant abdominal pain, vomiting, scleral icterus, jaundice, or dark urine on AQVESME treatment to their healthcare provider for further evaluation [see *Warnings and Precautions* (5.1)].

AQVESME REMS

AQVESME is only available through a restricted program called the AQVESME REMS [see *Warnings and Precautions* (5.2)].

Inform the patient of the following notable requirements:

- Patients must enroll in the REMS and comply with the REMS requirements.

AQVESME is available only from certified pharmacies participating in the REMS. Therefore, provide patients with the telephone number and website for information on how to obtain AQVESME.

Drug Interactions

Advise patients to inform their healthcare providers of all concomitant medications, including over-the-counter medications, vitamins, and herbal products [see *Drug Interactions* (7)].

Dosing and Storage Instructions

- Instruct patients to swallow the tablets whole with or without food and not to split, crush, chew, or dissolve the tablets.

- Advise patients if a dose of AQVESME is missed by 4 hours or less, to take the scheduled dose as soon as possible. If a dose of AQVESME is missed by more than 4 hours, advise the patient to not take a replacement dose and wait until the next scheduled dose.
- Advise patients to store AQVESME in a refrigerator at 2°C to 8°C (36°F to 46°F). Advise patients AQVESME may be stored at room temperature for up to 3 months. If removed from the refrigerator, advise the patient to store AQVESME at room temperature, 20°C to 25°C (68°F to 77°F), and record the discard date in the space provided in the blister wallet and/or the carton. The discard date is 3 months after removal of the tablets from the refrigerator. Advise the patient to discard the tablets by the written discard date or by the expiration date, whichever occurs first. Advise patients to store the blister wallets in the original carton until use.

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Manufactured for and Distributed by:

Agios Pharmaceuticals, Inc.
Cambridge, MA 02139

AG-PI-00X

MEDICATION GUIDE
AQVESME (ak ves' mee)
(mitapivat)
tablets, for oral use

What is the most important information I should know about AQVESME?

AQVESME can cause serious side effects, including:

- **Liver injury.** AQVESME can cause serious liver injury. Liver injury has happened in people with thalassemia within the first 6 months of treatment with AQVESME. Your healthcare provider will do blood tests to check your liver before you start treatment with AQVESME, every 4 weeks for the first 24 weeks of treatment, and as needed. Your healthcare provider may temporarily or permanently stop your treatment with AQVESME if you have abnormal liver blood tests. Tell your healthcare provider right away if you develop any new or worsening signs or symptoms of liver problems including:
 - loss of appetite
 - nausea
 - pain in the upper right side of your stomach area
 - vomiting
 - yellowing of the skin or white part of your eyes (jaundice)
 - dark-colored urine
- **Because of the risk of liver injury, AQVESME is only available through a restricted program called the AQVESME Risk Evaluation and Mitigation Strategy (REMS).**
 - Your healthcare provider must be enrolled in the AQVESME REMS for you to be prescribed AQVESME.
 - Before you start treatment with AQVESME, you must enroll in the AQVESME REMS. Talk to your healthcare provider about how to enroll in the AQVESME REMS.
 - Before you take AQVESME, your healthcare provider will make sure you understand how to take AQVESME safely, which will include liver tests when advised by your healthcare provider. Your healthcare provider will counsel you on the risk of liver injury and the REMS requirements.
 - AQVESME can only be dispensed by a certified pharmacy that participates in the AQVESME REMS. Your healthcare provider can give you information on how to find a certified pharmacy.
 - If you have any questions about the AQVESME REMS, ask your healthcare provider, go to www.aqvesmerems.com or call 1-800-625-9951.

See “What are the possible side effects of AQVESME?” for more information about side effects.

What is AQVESME?

AQVESME is a prescription medicine used to treat anemia (low red blood cells) in adults with alpha- or beta-thalassemia.

It is not known if AQVESME is safe and effective in children.

Before taking AQVESME, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems, such as cirrhosis.
- are pregnant or plan to become pregnant. It is not known if AQVESME will harm your unborn baby. Tell your healthcare provider right away if you become pregnant or think that you are pregnant during treatment with AQVESME.
- are breastfeeding or plan to breastfeed. It is not known if AQVESME passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with AQVESME.

Tell your healthcare provider about all the medicines that you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

- Make sure to tell your healthcare provider if you take or use hormonal birth control (contraceptives). If you take or use hormonal birth control (except for intrauterine systems containing levonorgestrel), it may not work as well during treatment with AQVESME. Use a different type of birth control or use an additional nonhormonal birth control method (such as condoms) during treatment with AQVESME and for 28 days after stopping treatment with AQVESME.
- AQVESME and certain other medicines may affect each other and cause side effects.
- AQVESME may affect the way other medicines work, and other medicines may affect how AQVESME works.

Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How should I take AQVESME?

- Take AQVESME exactly as your healthcare provider tells you to take it.
- Take AQVESME with or without food.

- Swallow AQVESME tablets whole. Do not split, crush, chew, or dissolve the tablets.
- If you miss a dose of AQVESME by 4 hours or less, take your dose as soon as possible. If more than 4 hours have passed since your regularly scheduled dose, do not take the missed dose and wait for the next dose. Return to your normal schedule at the next dose.

What are the possible side effects of AQVESME?

AQVESME can cause serious side effects:

- See “**What is the most important information I should know about AQVESME?**”

The most common side effects of AQVESME include headache and trouble sleeping (insomnia).

These are not all of the possible side effects of AQVESME.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AQVESME?

- Store AQVESME in a refrigerator between 36°F to 46°F (2°C to 8°C).
- You may also store AQVESME at room temperature between 68°F to 77°F (20°C to 25°C) for up to 3 months. If you remove AQVESME from the refrigerator, store AQVESME at room temperature.
 - Write the discard (throw away) date in the space provided on the blister wallet and the carton. The discard date is 3 months after you remove the tablets from the refrigerator.
 - Throw away AQVESME if not used by the written discard date or by the expiration date, whichever happens first.
- Store the blister wallets in the original carton until use.

Keep AQVESME and all medicines out of the reach of children.

General information about the safe and effective use of AQVESME.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use AQVESME for a condition for which it was not prescribed. Do not give AQVESME to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about AQVESME that is written for health professionals.

What are the ingredients in AQVESME?

Active ingredients: mitapivat

Inactive ingredients: croscarmellose sodium, mannitol, microcrystalline cellulose, and sodium stearyl fumarate.

The tablet film-coating contains: FD&C Blue No. 2, hypromellose, lactose monohydrate, titanium dioxide, triacetin, and macrogol/PEG.

The tablet printed with blue ink contains: ammonium hydroxide, FD&C Blue No. 1, isopropyl alcohol, n-butyl alcohol, propylene glycol, shellac glaze, and titanium dioxide.

Manufactured for and Distributed by: Agios Pharmaceuticals, Inc., Cambridge, MA 02139

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For more information, visit www.aqvesme.com or call 1-833-228-8474.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PYRUKYND safely and effectively. See full prescribing information for PYRUKYND.

PYRUKYND® (mitapivat) tablets, for oral use
Initial U.S. Approval: 2022

RECENT MAJOR CHANGES

Warnings and Precautions, Hepatocellular Injury in Another Condition (5.2)
01/2025

INDICATIONS AND USAGE

PYRUKYND is a pyruvate kinase activator indicated for the treatment of hemolytic anemia in adults with pyruvate kinase (PK) deficiency. (1)

DOSAGE AND ADMINISTRATION

- Starting dosage: 5 mg orally twice daily with or without food. (2.1)
- See Full Prescribing Information for dose titration and taper schedule. (2.1, 2.3)
- The tablet should be swallowed whole. (2.1)

DOSAGE FORMS AND STRENGTHS

Tablets: 5 mg, 20 mg, and 50 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Acute Hemolysis: Avoid abrupt interruption or abrupt discontinuation of PYRUKYND to minimize the risk of acute hemolysis. A gradual reduction in dosing rather than abrupt cessation is recommended when possible. (5.1)
- Hepatocellular Injury in Another Condition: Obtain liver tests prior to the initiation of PYRUKYND and monthly thereafter for the first 6 months and as clinically indicated. Interrupt PYRUKYND if clinically significant increases in liver tests are observed or alanine aminotransferase is >5 times the upper limit of normal (ULN). Discontinue PYRUKYND if hepatic injury due to PYRUKYND is suspected. (5.2)

ADVERSE REACTIONS

The most common adverse reactions including laboratory abnormalities ($\geq 10\%$) in patients with PK deficiency were estrone decreased (males), increased urate, back pain, estradiol decreased (males), and arthralgia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Agios Pharmaceuticals at 1-833-228-8474 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong CYP3A Inhibitors and Inducers: Avoid concomitant use. (7.1)
- Moderate CYP3A Inhibitors: Do not titrate PYRUKYND beyond 20 mg twice daily. (7.1)
- Moderate CYP3A Inducers: Consider alternatives that are not moderate inducers. If there are no alternatives, adjust PYRUKYND dosage. (7.1)
- Sensitive CYP3A, CYP2B6, CYP2C substrates including hormonal contraceptives: Avoid concomitant use with substrates that have narrow therapeutic index. (7.2)
- UGT1A1 Substrates: Avoid concomitant use with substrates that have narrow therapeutic index. (7.2)
- P-gp Substrates: Avoid concomitant use with substrates that have narrow therapeutic index. (7.2)

USE IN SPECIFIC POPULATIONS

Hepatic Impairment: Avoid use of PYRUKYND in patients with moderate or severe hepatic impairment. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

- INDICATIONS AND USAGE
- DOSAGE AND ADMINISTRATION
 - Recommended Dosage
 - Missed Dose
 - Interruption or Discontinuation
 - Recommended Dosage for Drug Interactions
 - Dose Modifications for Adverse Reactions and Hemoglobin Levels Above Normal
- DOSAGE FORMS AND STRENGTHS
- CONTRAINDICATIONS
- WARNINGS AND PRECAUTIONS
 - Acute Hemolysis with Abrupt Treatment Interruption
 - Hepatocellular Injury in Another Condition
- ADVERSE REACTIONS
 - Clinical Trials Experience
- DRUG INTERACTIONS
 - Effect of Other Drugs on PYRUKYND
 - Effect of PYRUKYND on Other Drugs

- USE IN SPECIFIC POPULATIONS
 - Pregnancy
 - Lactation
 - Pediatric Use
 - Geriatric Use
 - Hepatic Impairment
- DESCRIPTION
- CLINICAL PHARMACOLOGY
 - Mechanism of Action
 - Pharmacodynamics
 - Pharmacokinetics
- NONCLINICAL TOXICOLOGY
 - Carcinogenesis, Mutagenesis, Impairment of Fertility
- CLINICAL STUDIES
- HOW SUPPLIED/STORAGE AND HANDLING
- PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

PYRUKYND is indicated for the treatment of hemolytic anemia in adults with pyruvate kinase (PK) deficiency.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

PYRUKYND is taken with or without food and swallowed whole. Do not split, crush, chew, or dissolve the tablets.

The starting dosage for PYRUKYND is 5 mg orally twice daily. To gradually increase hemoglobin (Hb), titrate PYRUKYND from 5 mg twice daily to 20 mg twice daily, and then to the maximum recommended dose of 50 mg twice daily, with these dose increases occurring every 4 weeks (see Table 1). Assess Hb and transfusion requirement before increasing to the next dose level, as some patients may reach and maintain normal Hb at 5 mg twice daily or 20 mg twice daily.

Discontinue PYRUKYND if no benefit has been observed by 24 weeks, based on the hemoglobin and hemolysis laboratory results and transfusion requirements.

Table 1: Dose Titration Schedule

Duration	Dosage
Week 1 through Week 4	5 mg twice daily
Week 5 through Week 8	If Hb is below normal range or patient has required a transfusion within the last 8 weeks: • Increase to 20 mg twice daily and maintain for 4 weeks. If Hb is within normal range and patient has not required a transfusion within the last 8 weeks: • Maintain 5 mg twice daily.
Week 9 through Week 12	If Hb is below normal range or patient has required a transfusion within the last 8 weeks: • Increase to 50 mg twice daily and maintain thereafter. If Hb is within normal range and patient has not required a transfusion within the last 8 weeks: • Maintain current dose (5 mg twice daily or 20 mg twice daily).
Maintenance	If Hb decreases, consider up-titration to the maximum of 50 mg twice daily as per the above schedule.

2.2 Missed Dose

If a dose of PYRUKYND is missed by 4 hours or less, administer the dose as soon as possible. If a dose of PYRUKYND 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.

2.3 Interruption or Discontinuation

To reduce the risk of acute hemolysis, avoid abrupt interruption or abrupt discontinuation of PYRUKYND when possible [see *Warnings and Precautions (5.1)*]. Taper the dose to gradually

discontinue the medication (see Table 2). Monitor patients for signs of acute hemolysis and worsening of anemia.

Table 2: Dose Taper Schedule

Current Dose	Dose Taper Schedule		
	Day 1-7	Day 8-14	Day 15
5 mg twice daily	5 mg once daily	Discontinue	N/A
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	Discontinue

Abbreviations: N/A = not applicable.

2.4 Recommended Dosage for Drug Interactions

Moderate CYP3A Inhibitors

Monitor Hb and for increased risks of adverse reactions from PYRUKYND. When used with a moderate CYP3A inhibitor, do not titrate PYRUKYND beyond 20 mg twice daily [*see Drug Interactions (7.1) and Clinical Pharmacology (12.3)*].

Moderate CYP3A Inducers

Consider alternative therapies that are not moderate CYP3A inducers during treatment with PYRUKYND. If there are no alternative therapies, monitor Hb and titrate beyond the 50 mg twice daily dose, if necessary, but do not exceed a maximum recommended dose of 100 mg twice daily [*see Drug Interactions (7.1) and Clinical Pharmacology (12.3)*].

2.5 Dose Modifications for Adverse Reactions and Hemoglobin Levels Above Normal

If a dose reduction is required because of an adverse reaction or tolerability, or for Hb above normal, the dose may be reduced to the next lower dose level, 20 mg twice daily or 5 mg twice daily.

If a patient needs to discontinue PYRUKYND, the dose taper schedule (Table 2) 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 stopped without taper and patients should be monitored for signs of acute hemolysis.

3 DOSAGE FORMS AND STRENGTHS

- 5 mg tablets: round, blue, film-coated tablets with "M5" printed on one side.
- 20 mg tablets: round, blue, film-coated tablets with "M20" printed on one side.
- 50 mg tablets: oblong, blue, film-coated tablets with "M50" printed on one side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Acute Hemolysis with Abrupt Treatment Interruption

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 [*see Dosage and Administration (2.3, 2.6)*]. 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.

5.2 Hepatocellular Injury in Another Condition

In patients with another condition treated with mitapivat at a higher dose than that recommended for patients with PK deficiency, liver injury has been observed. These events were characterized by a time to onset within the first 6 months of treatment with peak elevations of alanine aminotransferase of $>5\times\text{ULN}$ with or without jaundice. All patients discontinued treatment with PYRUKYND, and these events improved upon treatment discontinuation.

Obtain liver tests prior to the initiation of PYRUKYND and monthly thereafter for the first 6 months and as clinically indicated. Interrupt PYRUKYND if clinically significant increases in liver tests are observed or alanine aminotransferase is >5 times the upper limit of normal (ULN). Discontinue PYRUKYND if hepatic injury due to PYRUKYND is suspected.

6 ADVERSE REACTIONS

The following clinically significant adverse reaction is described elsewhere in labeling:

- Acute Hemolysis with Abrupt Treatment Discontinuation [see *Warnings and Precautions (5.1)*].
- Hepatocellular Injury in Another Condition [see *Warnings and Precautions (5.2)*].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 155 patients received PYRUKYND, 79% of whom were exposed for longer than 24 weeks. PYRUKYND was administered up to 50 mg orally twice daily in 67 patients with PK deficiency in the ACTIVATE trial (N=40) and the ACTIVATE-T trial (N=27) [see *Clinical Studies (14)*].

ACTIVATE Trial

In the ACTIVATE trial patients with PK deficiency who were not regularly transfused received PYRUKYND in incremental doses up to 50 mg twice daily (N=40) or placebo (N=39).

Serious adverse reactions occurred in 10% of patients receiving PYRUKYND in the ACTIVATE Trial, including atrial fibrillation, gastroenteritis, rib fracture, and musculoskeletal pain, which each occurred in 1 patient.

In the ACTIVATE trial, the most common adverse reactions including laboratory abnormalities ($\geq 10\%$) in patients with PK deficiency were estrone decreased (males), increased urate, back pain, estradiol decreased (males), and arthralgia.

Table 3 summarizes the adverse reactions in the ACTIVATE trial.

Table 3: Adverse Reactions ($\geq 5\%$) in Patients Receiving PYRUKYND in ACTIVATE

Adverse Reactions	PYRUKYND (N=40)		Placebo (N=39)	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Back pain ^a	15%	0	8%	0

Arthralgia ^b	10%	0	5%	0
Hypertriglyceridemia ^c	8%	5%	3%	0
Gastroenteritis	8%	3%	0	0
Hot flush ^d	8%	0	0	0
Oropharyngeal pain	8%	0	5%	0
Hypertension	5%	5%	0	0
Arrhythmia ^e	5%	0	0	0
Breast discomfort	5%	0	0	0
Constipation	5%	0	0	0
Dry mouth ^f	5%	0	0	0
Paresthesia	5%	0	0	0

Grades: Per the CTCAE definition.

Grouped Term Definitions

^a Includes back pain, sciatica, and flank pain.

^b Includes arthralgia and joint swelling.

^c Includes hypertriglyceridemia and blood triglycerides increased.

^d Includes hot flush and flushing.

^e Includes arrhythmia, tachycardia, heart rate increased and atrial fibrillation.

^f Includes dry mouth and dry lip.

Laboratory abnormalities of PYRUKYND included increased urate (15%).

Variations in Reproductive Hormones

In ACTIVATE, increases in serum testosterone and decreases in serum estrone and estradiol were observed in men receiving PYRUKYND (Table 4). These changes in hormones persisted throughout the study period. In patients who discontinued PYRUKYND and had follow-up hormone measurements, the hormone changes returned close to the baseline levels 28 days after discontinuing PYRUKYND. In female patients, sex hormone analysis was limited due to physiologic variations in hormones during the menstrual cycle and the use of hormonal contraceptives.

Table 4: Laboratory Abnormalities in Reproductive Hormones in Men Receiving PYRUKYND

	ACTIVATE	
Parameter	PYRUKYND (16 males) n (%)	Placebo (15 males)n (%)
<i>Reproductive hormone analyses^a</i>		
Estrone decreased (males)	9 (56.3)	0
Estradiol decreased (males)	2 (12.5)	1 (6.7)
Blood testosterone increased (males)	1 (6.3)	1 (6.7)

^a Decreases in estrone and estradiol to below the lower limit of the reference range and increases in testosterone to above the upper limit of the reference range where baseline was within normal limits.

ACTIVATE-T Trial

The adverse reactions reported in the population of patients who were regularly transfused (ACTIVATE-T) were consistent with that seen in ACTIVATE.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on PYRUKYND

Strong CYP3A Inhibitors	
Clinical Impact	• Co-administration of PYRUKYND with strong CYP3A inhibitors increased mitapivat plasma concentrations [see <i>Clinical Pharmacology (12.3)</i>]. • Increased mitapivat plasma concentrations may increase the risks of adverse reactions of PYRUKYND.
Prevention or Management	• Avoid co-administration of strong CYP3A inhibitors with PYRUKYND [see <i>Dosage and Administration (2.5)</i>].
Moderate CYP3A Inhibitors	
Clinical Impact	• Co-administration of PYRUKYND with moderate CYP3A inhibitors will increase mitapivat plasma concentrations [see <i>Clinical Pharmacology (12.3)</i>].
Prevention or Management	• Monitor Hb and for increased risks of adverse reactions with PYRUKYND. • Do not titrate PYRUKYND beyond 20 mg twice daily [see <i>Dosage and Administration (2.5)</i>].
Strong CYP3A Inducers	
Clinical Impact	• Co-administration of PYRUKYND with strong CYP3A inducers decreased mitapivat plasma concentrations [see <i>Clinical Pharmacology (12.3)</i>]. • Decreased mitapivat plasma concentrations will reduce the efficacy of PYRUKYND.
Prevention or Management	• Avoid co-administration of strong CYP3A inducers with PYRUKYND [see <i>Dosage and Administration (2.5)</i>].
Moderate CYP3A Inducers	
Clinical Impact	• Co-administration of PYRUKYND with moderate CYP3A inducers will decrease mitapivat plasma concentrations [see <i>Clinical Pharmacology (12.3)</i>].
Prevention or Management	• Consider alternative therapies that are not moderate CYP3A inducers during treatment with PYRUKYND. If there are no alternative therapies, monitor Hb and titrate beyond 50 mg twice daily, if necessary, but do not exceed a maximum recommended dose of 100 mg twice daily [see <i>Dosage and Administration (2.5)</i>].

7.2 Effect of PYRUKYND on Other Drugs

CYP3A Substrates	
Clinical Impact	• PYRUKYND induces CYP3A. Co-administration of PYRUKYND will decrease systemic concentrations of drugs that are sensitive CYP3A substrates, including hormonal contraceptives (e.g., ethinyl estradiol) [see <i>Clinical Pharmacology</i> (12.3)].
Prevention or Management	• 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.
CYP2B6 and CYP2C Substrates	
Clinical Impact	• PYRUKYND induces CYP2B6, CYP2C8, CYP2C9, and CYP2C19 enzymes <i>in vitro</i>, and may decrease systemic concentrations of drugs that are sensitive substrates of these enzymes [see <i>Clinical Pharmacology</i> (12.3)].
Prevention or Management	• Monitor patients for loss of therapeutic effect of sensitive substrates of these enzymes with narrow therapeutic index when co-administered with PYRUKYND.
UGT1A1 Substrates	
Clinical Impact	• PYRUKYND induces UGT1A1 <i>in vitro</i> and may decrease systemic concentrations of drugs that are UGT1A1 substrates [see <i>Clinical Pharmacology</i> (12.3)].
Prevention or Management	• Monitor patients for loss of therapeutic effect of UGT1A1 substrates with narrow therapeutic index when co-administered with PYRUKYND.
P-gp Substrates	
Clinical Impact	• PYRUKYND inhibits the P-gp transporter <i>in vitro</i> and may increase systemic concentrations of drugs that are P-gp substrates [see <i>Clinical Pharmacology</i> (12.3)].
Prevention or Management	• Monitor patients for adverse reactions of P-gp substrates with narrow therapeutic index when co-administered with PYRUKYND.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from clinical trials of PYRUKYND are insufficient to evaluate for a drug- associated

risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes.

In animal reproduction studies, mitapivat orally administered twice daily to pregnant rats and rabbits during organogenesis was not teratogenic at doses up to 13 and 3 times the maximum recommended human dose (MRHD) of 50 mg twice daily, respectively. Mitapivat administered orally to pregnant rats twice daily during organogenesis through lactation did not result in adverse developmental effects at doses up to 13 times the MRHD (*see Data*).

The estimated background risk of major birth defects for the indicated population is unknown. Estimated frequencies for other important background risks in the population are as follows: miscarriage 18%, growth retardation 24%, preterm birth 56%. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal Risk

Untreated PK deficiency in pregnant women may precipitate acute hemolysis, pre-term labor, miscarriage and severe anemia requiring frequent transfusion. Additionally, preeclampsia and severe hypertension have been reported.

Data

Animal Data

In an embryo-fetal development study in rats, mitapivat was administered at doses of 5, 10, 25, and 100 mg/kg twice daily by oral gavage during the period of organogenesis (gestation days 6 to 17). There was a statistically significant 14% decrease in maternal net body weight gain at the high dose with associated decrease in food consumption. Enlarged or fused placenta and/or a distended amniotic sac, an increase in post-implantation loss (early and late resorptions), a decrease in the mean number of viable fetuses, lower mean fetal weights, and external, visceral, and skeletal malformations were observed at the high dose (100 mg/kg twice daily, 63 times the MRHD, based on area under the plasma drug concentration-time curve [AUC]). No maternal or embryo-fetal toxicity was observed up to 25 mg/kg twice daily (13 times the MRHD, based on AUC).

In an embryo-fetal development study in rabbits, mitapivat was administered at doses of 12.5, 30, and 62.5 mg/kg twice daily by oral gavage during the period of organogenesis (gestation days 7 to 20). Lower fetal weight was observed at 62.5 mg/kg twice daily (3 times MRHD, based on AUC) and correlated with reduced maternal body weight gain. No effects on fetal morphology were observed.

In a pre- and post-natal development study in rats, mitapivat was administered at doses of 5, 10, 25, and 100 mg/kg twice daily by oral gavage during the period of organogenesis and continuing to weaning (gestation day 7 to lactation day 20). Dystocia was observed at ≥ 25 mg/kg twice daily (≥ 13 x MRHD, based on AUC). At 100 mg/kg twice daily (63x MRHD, based on AUC) decreased maternal body weight gain, prolonged parturition, and dystocia occurred and resulted in maternal mortality, complete litter loss, decreased pup viability and decreased pup body weight. No adverse effects on pup growth and development, and reproductive performance were observed up to 50 mg/kg (13 times the MRHD, based on AUC).

8.2 Lactation

Risk Summary

There are no data on the presence of PYRUKYND or its metabolites in human or animal milk, the

effects on the breastfed child, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PYRUKYND and any potential adverse effects on the breastfed child from PYRUKYND or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

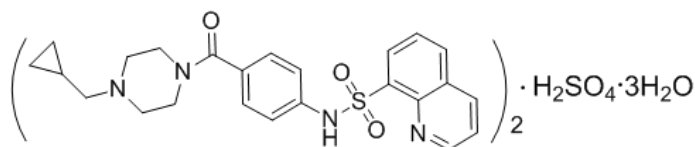
Clinical studies of PYRUKYND did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects.

8.6 Hepatic Impairment

Avoid use of PYRUKYND in patients with moderate and severe hepatic impairment [*see Warnings and Precautions (5.2)*]. Mitapivat undergoes extensive hepatic metabolism. In patients with moderate and severe hepatic impairment, there is a potential increase in the systemic exposure of mitapivat [*see Clinical Pharmacology (12.3)*].

11 DESCRIPTION

The active ingredient of PYRUKYND is mitapivat, a pyruvate kinase activator, present as mitapivat sulfate. The chemical name of mitapivat sulfate is 8-quinolinesulfonamide, N-[4-[(cyclopropylmethyl)-1-piperazinyl]carbonyl]phenyl]-, sulfate, hydrate (2:1:3). The chemical structure of mitapivat sulfate is:



The molecular formula is $(C_{24}H_{26}N_4SO_3)_2 \cdot H_2SO_4 \cdot 3H_2O$, and the molecular weight is 1053.23 for mitapivat sulfate. Mitapivat sulfate is a white to off-white solid and is slightly soluble in water.

PYRUKYND is available as 5 mg, 20 mg, and 50 mg tablets for oral administration. Each tablet contains 5 mg, 20 mg, or 50 mg mitapivat free base, provided as 5.85 mg, 23.4 mg, or 58.5 mg, respectively, of the sulfate hydrate salt, and the following inactive ingredients: croscarmellose sodium, mannitol, microcrystalline cellulose, and sodium stearyl fumarate. The tablet film coating contains the inactive ingredients FD&C Blue No. 2, hypromellose, lactose monohydrate, titanium dioxide, and triacetin. The tablets are imprinted with black ink containing the inactive ingredients ammonium hydroxide, ferrousferic oxide, isopropyl alcohol, n-butyl alcohol, propylene glycol, and shellac glaze.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Mitapivat 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.

12.2 Pharmacodynamics

Mitapivat decreases 2,3 diphosphoglycerate (2,3-DPG) and increases ATP in healthy volunteers.

Cardiac Electrophysiology

At a dose 6 times the maximum recommended dose, mitapivat did not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Mitapivat exposure increased in an approximately dose proportional manner over the clinically relevant dose range of 5 mg to 50 mg twice daily.

The population pharmacokinetic model simulated $C_{\max}$, C_{trough} , AUC_{0-12} and accumulation ratio of mitapivat at recommended dosages are listed in the table below.

Table 5: Steady State Mitapivat Exposure at Recommended Dosages^a

Mitapivat Dosage	$C_{\max}$ (ng/mL)	C_{trough} (ng/mL)	AUC_{0-12} (ng*h/mL)	Accumulation Ratio
5 mg twice daily	101.2 (17%)	10.1 (74%)	450.4 (28%)	1.2
20 mg twice daily	389.9 (18%)	32.3 (77%)	1623.8 (28%)	1.1
50 mg twice daily	935.2 (18%)	62.1 (80%)	3591.4 (28%)	1.0

^a Pharmacokinetic parameters are presented as geometric mean (CV%). The simulations were performed until 100 days after first dose. The interval of the last 12 hours was selected for steady state PK parameters calculation. Residual error was not included during simulation.

Absorption

Median $t_{\max}$ values at steady state were 0.5 to 1.0 hour post-dose across the dose range of 5 mg to 50 mg twice daily.

The absolute bioavailability after a single dose was approximately 73%.

Effect of Food

Following administration of a single dose of PYRUKYND in healthy subjects, a high-fat meal (approximately 900 to 1,000 total calories, with 500 to 600 calories from fat, 250 calories from carbohydrate, and 150 calories from protein) did not change the exposure (AUC_{inf}) of mitapivat, but reduced the rate of mitapivat absorption, with a 42% reduction in $C_{\max}$ and a delay in $t_{\max}$ of 2.3 hours when compared to dosing under fasted conditions.

Distribution

Mitapivat is highly protein bound (97.7%) in plasma with low RBC distribution (RBC-to-plasma ratio of 0.37). The mean volume of distribution at steady state (V_{ss}) was 42.5 L.

Elimination

The mean effective half-life ($t_{1/2}$) of mitapivat ranged from 3 to 5 hours following multiple dose administrations of 5 mg twice daily to 20 mg twice daily in patients with PK deficiency.

Population pharmacokinetics derived median CL/F at steady state was 11.5, 12.7, and 14.4 L/h for the 5 mg twice daily, 20 mg twice daily, and 50 mg twice daily regimens, respectively.

Metabolism

In vitro studies showed that mitapivat is primarily metabolized by CYP3A4. Following a single oral dose of 120 mg of radiolabeled mitapivat to healthy subjects, unchanged mitapivat was the major circulating component.

Excretion

After a single oral administration of radiolabeled mitapivat to healthy subjects, the total recovery of administered radioactive dose was 89.2%, with 49.6% in the urine (2.6% unchanged) and 39.6% in the feces (<1% unchanged).

Specific Populations

No clinically meaningful effects on the pharmacokinetics of mitapivat were observed based on age, sex, race, or body weight.

Pediatric Population

The pharmacokinetics of mitapivat in children and adolescents (<18 years old) have not been studied.

Hepatic Impairment

Mitapivat undergoes extensive hepatic metabolism. The pharmacokinetics of mitapivat were studied in adult subjects with moderate hepatic impairment (Child-Pugh Class B). After a single oral administration of 50 mg mitapivat, subjects with moderate hepatic impairment demonstrated 36% greater exposure (AUC_{∞}) to mitapivat, compared to subjects with normal hepatic function. Geometric mean C_{max} values were similar between the groups. There were no major changes to plasma protein binding or elimination half-life in subjects with moderate hepatic impairment relative to healthy controls. The pharmacokinetics of mitapivat in subjects with severe hepatic impairment (Child-Pugh Class C) have not been studied.

Renal Impairment

The effects of renal impairment on mitapivat pharmacokinetics were assessed with population pharmacokinetic analyses. Steady state AUC of mitapivat in patients with $eGFR$ 60 to <90 mL/min/1.73 m² was not significantly different compared to patients with $eGFR$ $\geq$ 90 mL/min/1.73 m². There are limited data available in patients with $eGFR$ 30 to <60 mL/min/1.73 m² and no data available in patients with $eGFR$ <30 mL/min/1.73 m².

Drug Interaction Studies

Clinical Studies and Model-Based Approaches

Effect of Strong CYP3A Inhibitors on PYRUKYND

Itraconazole (a strong CYP3A inhibitor) increased mitapivat AUC_{inf} and C_{max} by 4.9-fold and 1.7-fold, respectively, following a single PYRUKYND dose of 20 mg. Itraconazole increased mitapivat AUC_{0-12} and C_{max} by 3.6-fold and 2.2-fold, respectively, following PYRUKYND 50 mg twice daily. Ketoconazole (a strong CYP3A inhibitor) increased mitapivat AUC_{0-12} and C_{max} by approximately 3.9-fold and 2.4-fold, respectively, following PYRUKYND doses of 5, 20 or 50 mg twice daily.

Effect of Moderate CYP3A Inhibitors on PYRUKYND

Fluconazole (a moderate CYP3A inhibitor) increased mitapivat AUC_{0-12} and C_{max} by approximately 2.6-fold and 1.6-fold, respectively, following PYRUKYND doses of 5, 20 or 50 mg twice daily.

Effect of Strong CYP3A Inducers on PYRUKYND

Rifampin (a strong CYP3A inducer) decreased mitapivat AUC_{inf} and C_{max} by 91% and 77%, respectively, following a single PYRUKYND dose of 50 mg. Rifampin decreased mitapivat AUC_{0-12} and C_{max} by approximately 95% and 85%, respectively, following PYRUKYND doses of 5, 20 or 50 mg twice daily.

Effect of Moderate CYP3A Inducers on PYRUKYND

Efavirenz (a moderate CYP3A4 inducer) decreased mitapivat AUC₀₋₁₂ and C_{max} by approximately 60% and 30%, respectively, following PYRUKYND doses of 5 or 20 mg twice daily. Efavirenz decreased mitapivat AUC₀₋₁₂ and C_{max} by 55% and 24%, respectively, following PYRUKYND doses of 50 mg twice daily.

Effect of PYRUKYND on CYP3A substrates

Midazolam (a CYP3A substrate) AUC_{inf} and C_{max} decreased by 21% and 19%, respectively, following co-administration of midazolam with PYRUKYND 5 mg twice daily. Midazolam AUC_{inf} and C_{max} decreased by 43% and 39%, respectively, following co-administration with PYRUKYND 20 mg twice daily, and 57% and 52%, respectively, with PYRUKYND 50 mg twice daily.

Effect of PYRUKYND on P-gp Substrates

Co-administration of PYRUKYND with drugs that are substrates of P-gp may result in a clinically relevant increase in plasma concentrations of these substrates.

In vitro Studies

CYP450 and UGT Enzymes

Mitapivat induces CYP2B6, CYP2C8, CYP2C9, CYP2C19, and UGT1A1.

Drug Transporter Systems

Mitapivat is a substrate and an inhibitor of P-gp.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Mitapivat was not carcinogenic in transgenic rasH2 mice up to the highest doses tested at 500 mg/kg/day in males and at 250 mg/kg/day in females when given orally for 26 weeks.

Mitapivat was not carcinogenic in rats when given orally up to 300 mg/kg/day in males and 200 mg/kg/day in females, at systemic exposures 47 times and >100 times the MRHD, respectively, based on AUC.

Mutagenesis

Mitapivat was not mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay. Mitapivat was not clastogenic in an *in vitro* human lymphocyte micronucleus assay or in an *in vivo* rat bone marrow micronucleus assay.

Fertility

In a fertility and early embryonic development study, oral administration of mitapivat twice daily in male rats prior to and during mating at doses up to 300 mg/kg/day, which represents 45 times the MRHD of 50 mg twice daily, based on AUC, did not result in adverse effects on fertility or reproductive function. In female rats, twice daily oral administration of mitapivat prior to mating and continuing through organogenesis, at doses up to 200 mg/kg/day, which represents 48 times the MRHD of 50 mg twice daily, based on AUC, did not result in adverse effects on fertility or reproductive function.

14 CLINICAL STUDIES

Patients with PK Deficiency

Patients Not Regularly Transfused

The efficacy of PYRUKYND was evaluated in ACTIVATE, a multinational, randomized, double-blind, placebo-controlled clinical study (NCT03548220) of 80 adults with PK deficiency 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 less than or equal to 10 g/dL. Patients who were homozygous for the c.1436G>A (p.R479H) variant or had 2 non-missense variants (without the presence of another missense variant) in the PKLR gene were excluded because these patients did not achieve Hb response (change from baseline in Hb ≥ 1.5 g/dL at >50% assessments) in the dose-ranging study.

Randomization was stratified by average screening Hb (<8.5 vs ≥ 8.5 g/dL) and PKLR gene variant category (missense/missense vs. missense/non-missense).

Among the 80 patients with PK deficiency, 40 patients were randomized to PYRUKYND. Following a period of dose titration up to 50 mg twice daily, patients continued a fixed dose of PYRUKYND for 12 weeks. Eighty-eight percent of patients were maintained on 50 mg twice daily.

The median duration of treatment with PYRUKYND was 24.1 weeks (range 23.6 to 27.4 weeks). Overall, 30 (75%) patients were exposed to PYRUKYND for >24 weeks and <28 weeks. Among the 80 randomized patients, the median age was 33 years (range 18 to 78) and 40% were male; race was reported in 88% of patients: 75% were White, 10% Asian, 1.3% Native Hawaiian/Other Pacific Islander and 1.3% were other races. The median baseline hemoglobin was 8.5 g/dL (range: 6.4 to 10.2 g/dL). There were 55 patients (69%) with the missense/missense PKLR gene variant category, and 25 patients (31%) with the missense/non-missense PKLR gene variant category. There were 58 patients (73%) who had a history of splenectomy. Complications and comorbidities associated with PK deficiency included iron overload with a median baseline ferritin of 479 ng/mL (range: 21 to 5890 ng/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 history of cholecystectomy in 58 patients (73%).

Efficacy was based upon Hb response, defined as a ≥ 1.5 g/dL increase in Hb from baseline sustained at 2 or more scheduled assessments (Weeks 16, 20, and 24) during the fixed dose period without transfusions. The efficacy results, including changes in markers of hemolysis are shown in Table 6.

Table 6: Efficacy Results in Patients with PK Deficiency Who Were Not Regularly Transfused (ACTIVATE)

Endpoint	PYRUKYND N=40	Placebo N=40	Difference ^{1, 2} p-value
Hb 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, 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
LDH (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

CI: confidence interval, Hb: hemoglobin, LDH: lactate dehydrogenase, LS Mean Change: least square mean change from baseline, SD: standard deviation

¹ All results are statistically significant.

² For Hb response, the difference is adjusted for randomization stratification factors, which included average screening Hb (<8.5, ≥8.5 g/dL) and PKLR gene variant category (missense/missense, missense/non-missense). The two-sided p-value is based on the Mantel-Haenszel stratum weighted method adjusting for the randomization stratification factors.

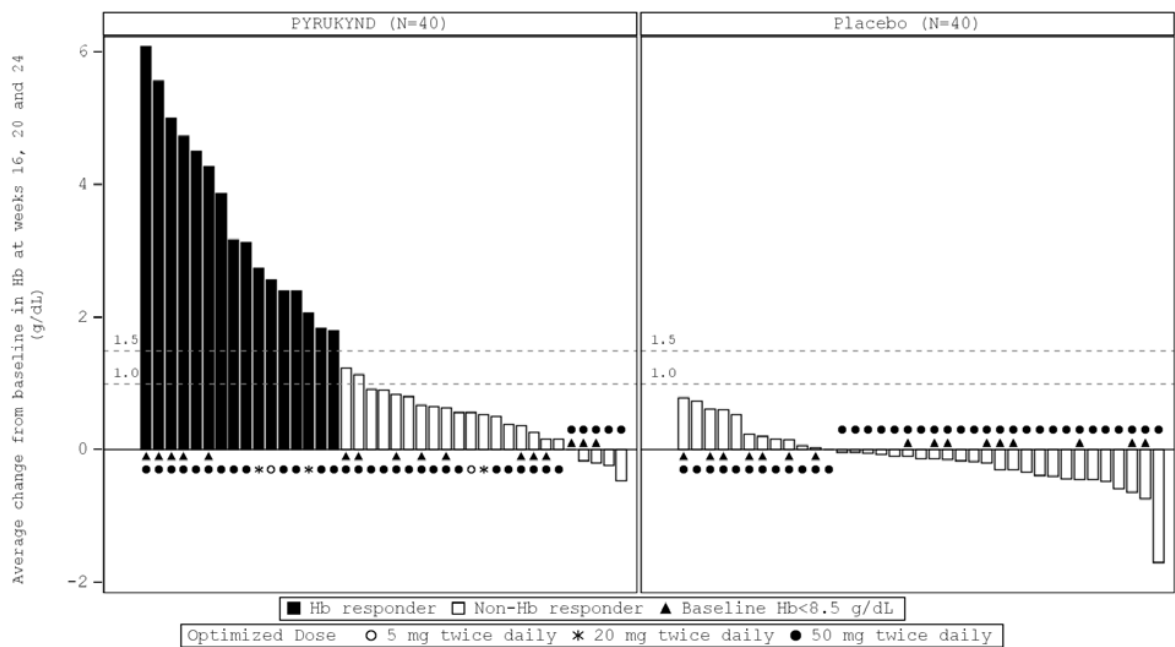
For the endpoints of average change from baseline at Weeks 16, 20, and 24 for hemoglobin, indirect bilirubin, reticulocytes, LDH, and haptoglobin, the two-sided p-value is based on the mixed-effect model repeat measurement (MMRM) method, which included change from baseline as the dependent variable, baseline as a covariate, and treatment arm, visit, treatment-by-visit interaction, and the randomization stratification factors as fixed factors and subject as the random effect. All scheduled visits were included in the model.

In ACTIVATE, the LS Mean change from baseline with PYRUKYND 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), assessed with the daily Pyruvate Kinase Deficiency Diary (PKDD) where lower scores represent less sign/symptom severity.

In ACTIVATE, the majority of PYRUKYND-treated patients experienced an increase in Hb, while the

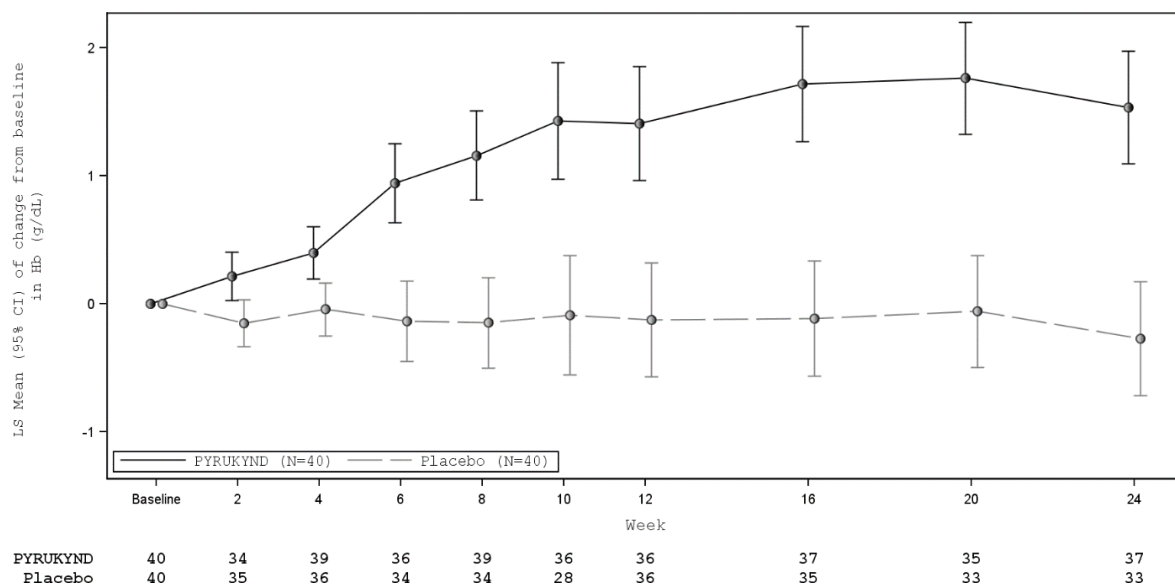
majority of patients in the placebo arm experienced a decrease in Hb as measured by average change from baseline at weeks 16, 20, and 24 (Figure 1).

Figure 1: Average Change at Weeks 16, 20, and 24 from Baseline in Hemoglobin (Hb) by Patient - All Randomized Patients (ACTIVATE)^a



^aApproximately 99% of all randomized patients completed 24 weeks of treatment.

Figure 2: LS Mean Change from Baseline in Hemoglobin Over Time - All Randomized Patients (ACTIVATE)



CI: confidence interval, Hb: hemoglobin, LS: least square

Fifteen of the 16 patients with a Hb response in ACTIVATE 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 ≥ 1.5 g/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 (range: 3.3, 18.4+).

Patients Who Were Regularly Transfused

The efficacy of PYRUKYND in patients with PK deficiency who were regularly transfused was evaluated in ACTIVATE-T, a multinational single-arm clinical trial (NCT03559699) of 27 adults with PK deficiency 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 (p.R479H) 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 50 mg twice daily, patients continued on a fixed dose of PYRUKYND for 24 weeks.

The median duration of treatment with PYRUKYND was 40.3 weeks (range 16.3 to 46.3 weeks). Overall, 20 (74%) patients were exposed to PYRUKYND for >40 weeks and <47 weeks. The median age was 36 years (range 18 to 68) and 26% were male; race was reported in 85% of patients: 74% were White and 11% Asian. The median baseline hemoglobin was 9.1 g/dL (range: 7.4 to 10.9 g/dL). Patients had a median of 9 transfusion episodes (range: 6 to 17 episodes) in the 52 weeks before the first dose of study treatment and a median of 7 red blood cell units transfused (range: 3 to 20 units) standardized to 24 weeks. There were 20 patients (74%) with the missense/missense PKLR gene variant category, and 7 patients (26%) with the missense/non-missense PKLR gene variant category. There were 21 patients (78%) who had a history of splenectomy. Patients had evidence of complications and comorbidities associated with PK deficiency including iron overload (median baseline ferritin was 1324 ug/L; range: 163 to 5357 ng/mL), 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 history of cholecystectomy in 23 patients (85%).

Efficacy was based on transfusion reduction response and was defined as $\geq 33\%$ reduction in the number of red blood cell (RBC) 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 Table 7.

Table 7: Efficacy Results in Patients with PK Deficiency Who Were Regularly Transfused (ACTIVATE-T)

Endpoints	PYRUKYND N=27
Patients with Transfusion Reduction Response	
n (%)	9 (33)
95% CI	(17, 54)
Patients who were Transfusion Free	
n (%)	6 (22)
95% CI	(9, 42)

CI: confidence interval, RBC: red blood cell CI is based on Clopper-Pearson method.

All 6 (22%) patients who were transfusion free in ACTIVATE-T remained transfusion free in a long-term extension study. The median duration of response for the 6 patients was 17 months (range: 11.5+, 21.8+).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

<u>PYRUKYND 28-Day Packs</u>			
Tablet Strength	Description	Imprint	NDC
5 mg	Round, blue, film-coated tablets	"M5" printed on one side	71334-205-05
20 mg	Round, blue, film-coated tablets	"M20" printed on one side	71334-210-20
50 mg	Oblong, blue, film-coated tablets	"M50" printed on one side	71334-215-50

<u>PYRUKYND Taper Packs</u>				
Tablet strength(s)	Blister Wallet Configuration	Tablet Description	Imprint	NDC
5 mg	5 mg blister wallet containing 7 tablets	round, blue, film-coated tablets	"M5" printed on one side	71334-220-11
20 mg and 5 mg	20 mg blister wallet containing 7 tablets	round, blue, film-coated tablets	"M20" printed on one side	71334-225-12
	5 mg blister wallet containing 7 tablets	round, blue, film-coated tablets	"M5" printed on one side	
50 mg and 20 mg	50 mg blister wallet containing 7 tablets	oblong, blue, film-coated tablets	"M50" printed on one side	71334-230-13
	20 mg blister wallet containing 7 tablets	round, blue, film-coated tablets	"M20" printed on one side	

Storage

Store at 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Store the blister wallets in the original carton until use.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Acute Hemolysis with Abrupt Treatment Interruption

Inform patients of the risk of developing acute hemolysis and subsequent anemia following abrupt interruption or discontinuation of PYRUKYND. Inform patients to follow their healthcare provider's instructions for discontinuing PYRUKYND. Upon discontinuing PYRUKYND, tell patients to immediately report any symptoms suggestive of acute hemolysis including jaundice, scleral icterus,

dark urine, dizziness, confusion, fatigue, or shortness of breath to their healthcare provider for further evaluation [see *Warnings and Precautions* (5.1)].

Hepatocellular Injury in Another Condition

Inform patients of the risk of hepatocellular injury observed in patients with another condition during the first 6 months of treatment with mitapivat at a higher dose than that recommended for patients with PK deficiency. Tell patients to immediately report any symptoms suggestive of liver injury including jaundice, dark urine, right upper quadrant pain, nausea, vomiting, or loss of appetite to their healthcare provider for further evaluation [see *Warnings and Precautions* (5.2)].

Drug Interactions

Advise patients to inform their healthcare providers of all concomitant medications, including over-the-counter medications, vitamins, and herbal products [see *Drug Interactions* (7)].

Dosing and Storage Instructions

- Instruct patients to swallow the tablets whole with or without food and not to split, crush, chew, or dissolve the tablets.
- Advise patients if a dose of PYRUKYND is missed by 4 hours or less, to take the scheduled dose as soon as possible. If a dose of PYRUKYND is missed by more than 4 hours, advise the patient to not take a replacement dose and wait until the next scheduled dose.

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Manufactured for and Distributed by:

Agios Pharmaceuticals, Inc.
Cambridge, MA 02139

AG-PI-004

PATIENT INFORMATION PYRUKYND (pye roo' kind) (mitapivat) tablets, for oral use
What is PYRUKYND? PYRUKYND is a prescription medicine used to treat low red blood cell counts caused by the early breakdown of red blood cells (hemolytic anemia) in adults with pyruvate kinase deficiency (PK Deficiency). It is not known if PYRUKYND is safe and effective in children.
Before taking PYRUKYND, tell your healthcare provider about all your medical conditions, including if you: • have liver problems. • are pregnant or plan to become pregnant. It is not known if PYRUKYND will harm your unborn baby. Tell your healthcare provider right away if you become pregnant or think that you are pregnant during treatment with PYRUKYND. • are breastfeeding or plan to breastfeed. It is not known if PYRUKYND passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with PYRUKYND. Tell your healthcare provider about all the medicines that you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. PYRUKYND and certain other medicines may affect each other causing side effects. PYRUKYND may affect the way other medicines work, and other medicines may affect how PYRUKYND works. Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.
How should I take PYRUKYND? • Take PYRUKYND exactly as your healthcare provider tells you to take it. • Take PYRUKYND with or without food. • Swallow PYRUKYND tablets whole. Do not split, chew, crush, or dissolve the tablets. • Do not change your dose or stop taking PYRUKYND without talking to your healthcare provider. Your healthcare provider will give you instructions for stopping PYRUKYND. See “What are the possible side effects of PYRUKYND?” • If you miss a dose of PYRUKYND by 4 hours or less, take your dose as soon as possible. If more than 4 hours have passed since your regularly scheduled dose, wait for the next dose. Return to your normal schedule at the next dose.
What are the possible side effects of PYRUKYND? PYRUKYND may cause serious side effects, including: • Rapid breakdown of red blood cells (acute hemolysis) has happened after suddenly interrupting or stopping treatment with PYRUKYND. You should not suddenly stop taking PYRUKYND. If you have to stop your treatment with PYRUKYND, your healthcare provider should monitor you closely. Tell your healthcare provider right away if you develop any signs or symptoms of breakdown of red blood cells including: ○ yellowing of your skin or the whites of your eyes (jaundice) ○ dark colored urine ○ dizziness ○ feeling tired ○ shortness of breath ○ confusion • Liver injury has happened in people with another condition during the first 6 months of treatment with mitapivat when given at a dose higher than recommended for people with PK deficiency. Your healthcare provider will do blood tests to check your liver before you start treatment with PYRUKYND, monthly for the first 6 months of treatment, and as needed. Your healthcare provider may temporarily or permanently stop your treatment with PYRUKYND if you have abnormal liver tests. Tell your healthcare provider right away if you develop any signs or symptoms of liver problems including: ○ yellowing of your skin or the whites of your eyes (jaundice) ○ dark colored urine ○ pain in the upper right side of your stomach area ○ nausea ○ vomiting ○ loss of appetite

The most common side effects of PYRUKYND include:

- decrease in reproductive hormone (estrone) in men
- decrease in reproductive hormone (estradiol) in men
- increased salt from uric acid (urate) blood test
- joint pain (arthralgia)
- back pain

These are not all of the possible side effects of PYRUKYND.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store PYRUKYND?

- Store PYRUKYND at room temperature between 68°F to 77°F (20°C to 25°C).
- Store the blister wallets in the original carton until use.

Keep PYRUKYND and all medicines out of the reach of children.

General information about the safe and effective use of PYRUKYND.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use PYRUKYND for a condition for which it was not prescribed. Do not give PYRUKYND to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about PYRUKYND that is written for healthcare professionals.

What are the ingredients in PYRUKYND?

Active ingredient: mitapivat

Inactive ingredients: croscarmellose sodium, mannitol, microcrystalline cellulose, and sodium stearyl fumarate.

The tablet film coating contains: FD&C Blue No. 2, hypromellose, lactose monohydrate, titanium dioxide, and triacetin.

The tablets printed with black ink contains: ammonium hydroxide, ferrosoferric oxide, isopropyl alcohol, n-butyl alcohol, propylene glycol, and shellac glaze.

Manufactured for and Distributed by:

Agios Pharmaceuticals, Inc.
Cambridge, MA 02139

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For more information, visit www.pyrukynynd.com or call 1-833-228-8474.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: 12/2025



Aqvesme™
(mitapivat) tablets

100 mg per tablet



Aqvesme™
(mitapivat) tablets

100 mg per tablet



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100 mg per tablet



Aqvesme™
(mitapivat) tablets

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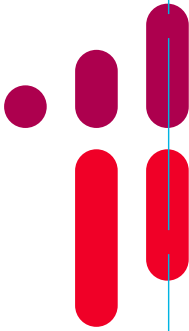
(b) (4)

NDC 71334-235-14 Rx Only

Aqvesme™
(mitapivat) tablets

100 mg per tablet

DISPENSE THE MEDICATION GUIDE
PROVIDED SEPARATELY
TO EACH PATIENT.
Swallow tablets whole. Do not split, crush,
chew, or dissolve the tablets.



Manufactured for and distributed by:
Agiros Pharmaceuticals, Inc.
Cambridge, MA 02139
agios

OPENING INSTRUCTIONS

- 1 Use thumb to **PUSH**
- 2 Turn package over, **PEEL** the raised tab on the back
- 3 Push tablet through the foil

Storage: Store in a refrigerator 2 °C to 8 °C (36 °F to 46 °F).

AQVESME™ may be stored at room temperature, 20 °C to 25 °C (68 °F to 77 °F) for up to 3 months. Write the discard date in the space provided. Discard the tablets if not used within 3 months or if the expiration date has passed, whichever occurs first.

Discard date (3 months after removal from refrigerator):
____/____/____.

Dispense and store the blister wallets in the original carton until use.

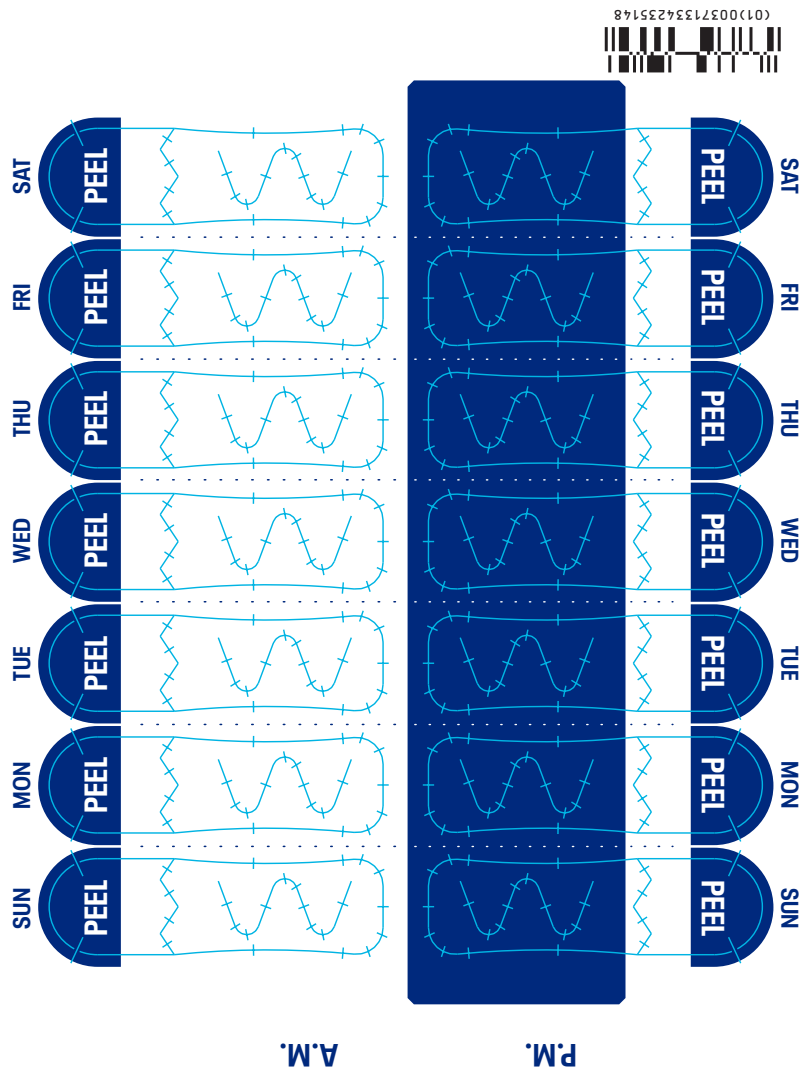
Keep out of the reach of children.

Take AQVESME™ exactly as prescribed by your healthcare provider.

Recommended Dosage: See prescribing information

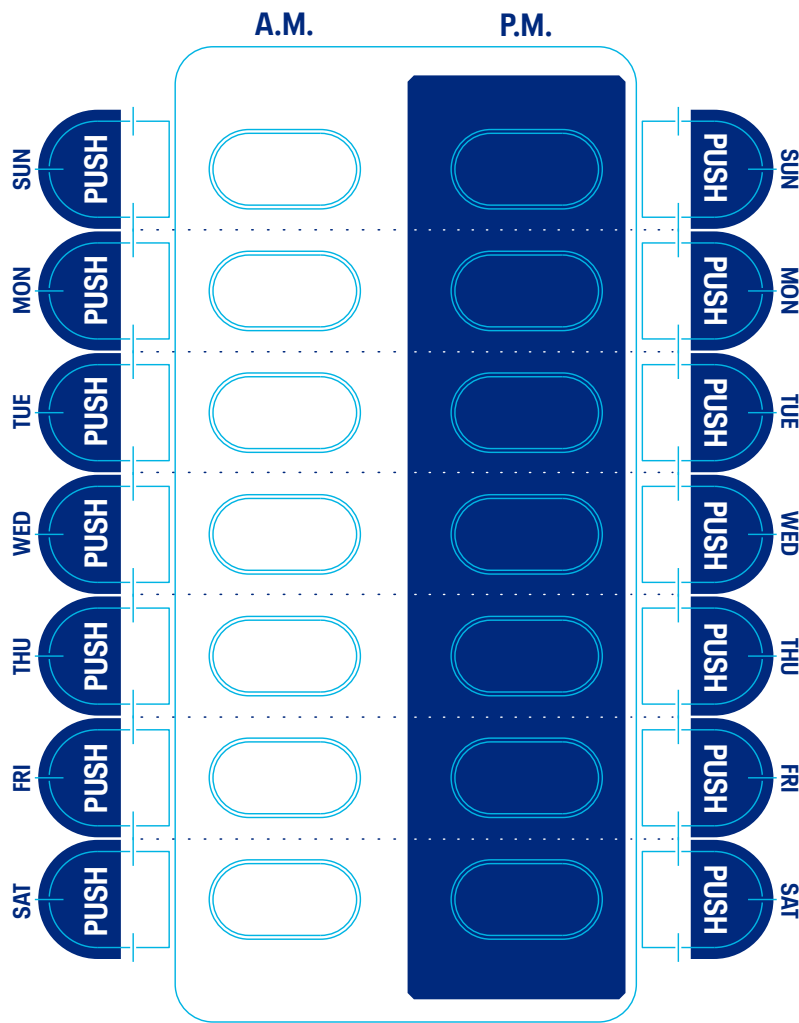
LOT XXXXXXX
EXP YYYY-MM

APCXXXX



Aqvesme™
(mitapivat) tablets

100 mg per tablet



Take all tablets as prescribed before starting the next blister wallet

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TANYA M WROBLEWSKI
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