New Drug Overview

Aqvesme (mitapivat)

PDL Category: Pyruvate Kinase Activators

Introduction

Disease Background:

- Thalassemia denotes a group of inherited hemoglobinopathies that began in certain areas of the world where malaria is (or was) endemic (*Benz Jr and Angelucci 2026a*).
  - One of the most frequent of the hemoglobinopathies, second to sickle cell disease, are the thalassemias.
  - Data suggests that approximately 5% globally has at least one thalassemia variant allele.
    - Alpha thalassemia is very common in Southern China, Malaysia, and Thailand. Mild versions are also frequently observed in patients with African ancestry.
    - Beta thalassemia is seen in Africa, with an approximate heterozygote frequency of about 3-4%.
- Thalassemia's are described by a decrease in production of the alpha or beta chains that make the hemoglobin molecule, which creates an imbalance in the normal alpha to beta chain ratio (*Benz Jr and Angelucci 2026a*).
  - Alpha thalassemia is a result of decreased production of alpha chains and accrual of beta-like chains.
  - Beta thalassemia is caused by decreased production of beta chains and an accrual of alpha chains.
    - Individuals with beta thalassemia can be either transfusion-dependent (need transfusions on a regular basis because of severe anemia and/or noteworthy complications of extramedullary hematopoiesis) or non-transfusion dependent (with anemia that does not need transfusions on a regular basis).
  - This imbalance steers to precipitation of the unpaired chains, which then results in destruction of developing red blood cell (RBC) precursors in the bone marrow. This ultimately may lead to erythropoiesis that is not effective and/or hemolysis with subsequent anemia and iron overload (*Benz and Angelucci 2026*).
- While some with thalassemia's are asymptomatic, some have profound abnormalities such as severe anemia, extramedullary hematopoiesis, skeletal and growth deficits, and iron overload with a reduced life expectancy without aggressive treatment (*Benz Jr and Angelucci 2026a*).
- The main concerns in managing thalassemia includes anemia treatment, reducing ineffective erythropoiesis, preventing excess iron stores, and treating complications of iron overload (*Benz and Angelucci 2026*).
  - The major treatments for anemia have included transfusions and luspatercept.
- Aqvesme was FDA approved in 2025.

Pharmacology/Usage

- Aqvesme (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.

Indications

Table 1. Food and Drug Administration Approved Indications

Indication	Aqvesme (mitapivat)
• For the treatment of anemia in adults with alpha- or beta-thalassemia.	✔

(Prescribing information: Aqvesme 2025)

- Information on indications, mechanism of action, pharmacokinetics, dosing, safety, and clinical efficacy summary has been obtained from the prescribing information for the individual products, except where noted otherwise.

Dosing and administration

Table 2. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Aqvesme (mitapivat)	Film-Coated Tablets -Do not split, crush, chew or dissolve tablets.	PO	BID with or without food. -Treatment 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 (eg, bleeding, surgery, other concomitant illnesses).	• If a dose is missed by 4 hours or less, administer the dose as soon as possible. If a dose is missed by more than 4 hours, do not administer a replacement dose and wait until the next scheduled dose. • Monitor for hepatocellular injury during Aqvesme treatment. • Prior to starting treatment, check liver tests (including ALT, AST, alkaline phosphatase, total bilirubin with fractionation) before the first dose. After the first dose, check liver tests every 4 weeks for 24 weeks and as clinically indicated. • Avoid use in patients with cirrhosis.

See the current prescribing information for full details.

Clinical Efficacy Summary

- The efficacy of Aqvesme was assessed in ENERGIZE-T, a multinational, randomized, double-blind, placebo-controlled study that included adult patients (N=258) with transfusion-dependent alpha- or beta-thalassemia, defined as having had 6 to 20 red blood cell (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).

- Of the patients (N=258) with transfusion-dependent alpha- or beta-thalassemia, 171 patients were randomized to receive Aqvesme 100mg BID 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 patients (60.5%) were exposed to Aqvesme for >48 weeks.
  - Among the randomized patients (N=258), the median age was 33.5 years (range 18 to 67), while 47.3% were male, 62% were from North America and Europe, and 60.1% were White. The baseline hemoglobin (median) was 9.0g/dL with the Aqvesme group and 8.9g/dL with placebo. The thalassemia genotype was 44% for beta/beta with Aqvesme and 45% with placebo, while the transfusion burden (RBC units, %) ≤12 was 32% for Aqvesme and 24% for placebo. 96% in the Aqvesme group had prior history of iron chelation compared to 100% in the placebo group, while 4.1% in the Aqvesme group had prior history of hydroxyurea as compared with 3.4% in the placebo group.
- Efficacy was based on 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.
  - Results are presented in the table below, which was adapted from the prescribing information.

Table 3. Efficacy results

Efficacy	Aqvesme (N=171)	Placebo (N=87)	Difference	
Endpoints	n (%)	n (%)	Adjusted Rate Difference (%)	p-value
≥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%	0.0003
Endpoints	n (%)	n (%)	Adjusted Rate Difference (%)	p-value
≥50% reduction from baseline in RBC units transfused in any consecutive 24 weeks	23 (13.5%)	2 (2.3%)	11.1%	0.0003
≥33% reduction from baseline in RBC units from week 13 through week 48	25 (14.6%)	1 (1.1%)	13.4%	<0.0001
≥50% reduction from baseline in RBC units from week 13 through week 48	13 (7.6%)	1 (1.1%)	6.4%	0.0056

- The efficacy of Aqvesme was assessed in ENERGIZE, a multinational, randomized, double-blind, placebo-controlled clinical study that included adults (N=194) 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 ≤10g/L.
  - Of the 194 patients with non-transfusion-dependent alpha- or beta-thalassemia, 130 patients were randomized to receive Aqvesme 100mg BID 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 patients (75%) were exposed to Aqvesme for >24 weeks.
    - Among the randomized patients (N=194), the median age was 41 years (range 18 to 69), while 36.6% were male and 56.2% were White. The baseline hemoglobin (median) was 8.4g/dL with the Aqvesme group and 8.4g/dL with placebo. The thalassemia genotype was 32% for alpha-thalassemia/HbH disease with Aqvesme and 31% with

placebo and 68% for beta-thalassemia in the Aqvesme group and 69% with placebo, while the transfusion burden (RBC units, %) 0 was 87.7% for Aqvesme and 84.4% for placebo. 35% in the Aqvesme group had prior history of iron chelation compared to 34% in the placebo group, while 8.5% in the Aqvesme group had prior history of hydroxyurea as compared with 9.4% in the placebo group.

- Efficacy was based upon Hb response, defined as a ≥1g/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).
  - Results are presented in the table below, which was adapted from the prescribing information.

Table 4. Efficacy results

Efficacy	Aqvesme (N=130)	Placebo (N=64)	Difference	
Endpoint	n (%)	n (%)	Adjusted Rate Difference (%)	p-value
Hb Response	55 (42.3%)	1 (1.6%)	40.9%	<0.0001
Endpoint	LS mean	LS mean	LS mean difference	p-value
Hemoglobin (g/dL)	0.86	-0.11	0.96	<0.0001
FACIT-Fatigue	4.85	1.46	3.40	0.0026

- Eighty-seven percent of patients in the Aqvesme arm experienced an increase from baseline in average Hb from weeks 12 through 24.
- Of the 55 patients with Hb response in the Aqvesme arm, the average increase in Hb was 1.6g/dL and the median duration of response was 19.6 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 [-0.62mg/dL] and lactate dehydrogenase [-24.28 U/L]).

Clinical guidelines

- Published guidelines do not currently include Aqvesme, as the guidelines were published before Aqvesme was FDA approved.
- **Thalassemia International Federation (TIF) 5th edition guidelines for the management of transfusion-dependent β-thalassemia** (*Musallam et al 2025, Taher et al 2025).*
  - For blood transfusion:
    - Confirm thalassemia diagnosis and obtain appropriate clinical and laboratory assessments.
    - Deciding to start long-term regular transfusion regimens should be driven by several criteria discussed in the guidelines.
    - Keep the post-transfusion hemoglobin below 13-15g/dL.
  - For iron overload and chelation:
    - Chelation therapy is an effective treatment option for improving survival, decreasing heart failure risk, and decreasing morbidities from transfusion-induced iron overload.
    - Chelation treatment can balance iron excretion with iron accumulation from transfusions when given at the appropriate dose and frequency.

- Hematopoietic cell transplantation (HCT) should be offered to transfusion-dependent β-thalassemia (TDT) patients, and gene manipulation is also discussed.
- Novel disease-modifying agents
  - Luspatercept is recommended in TDT adults for obtaining reduction in transfusion burden.

- **Thalassemia International Federation (TIF) guidelines for the management of alpha-thalassemia** (*Amid et al 2023*)
  - Note that Hb H is hemoglobin H disease and is a form of alpha thalassemia (*Benz and Angelucci 2026*).
  - Blood transfusions:
    - The goal of blood transfusion is to reestablish hemoglobin to baseline or somewhat higher. The choice to provide on-demand transfusion should be based on the patient's clinical status and clinical indication of course of acute illness.
    - The criteria to begin regular transfusions with HbH disease are not defined and typically based on expert opinion. The demand for ongoing regular transfusions should be assessed on a regular basis.
- Splenectomy can be considered with HbH disease in patients with moderately severe anemia, if have long-term complications of chronic hemolytic anemia, or if undergo frequent acute hemolytic events that require on-demand transfusion, or those with symptomatic splenomegaly.
- The main goal of iron overload treatment is to protect against organ toxicity.
- Regarding novel and emerging therapies for alpha-thalassemia, various agents are being studied in alpha thalassemia, and the most promising are luspatercept and mitapivat.

Safety summary

- **Contraindications:** None.

- **Box Warning:**
  - Aqvesme has a box warning regarding 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 treatment if hepatic injury is suspected.
    - 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.

- **Warnings and precautions:**
  - Aqvesme is available only through a restricted program under a REMS called the Aqvesme REMS, due to the risk of hepatocellular injury (see Box warning).
    - 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 by calling 1-800-625-9951.

- **Common adverse drug reactions**:
  - Listed % incidence for adverse drug reactions= reported % incidence for drug (Aqvesme) minus reported % incidence for placebo in the ENERGIZE study. Please note that an incidence of 0% means the incidence was the same as or less than comparator.
    - The most frequently reported adverse events included headache (13%) and insomnia (19.2%).
  - Listed % incidence for adverse drug reactions= reported % incidence for drug (Aqvesme) minus reported % incidence for placebo in the ENERGIZE-T study. Please note that an incidence of 0% means the incidence was the same as or less than comparator.
    - The most frequently reported adverse events included headache (14.9%) and insomnia (12.7%).

- **Drug interactions:**
  - Avoid the coadministration of strong CYP3A inhibitors with Aqvesme.
  - Avoid the coadministration of moderate CYP3A inhibitors with Aqvesme.
  - Avoid the coadministration of strong CYP3A inducers with Aqvesme.
  - Consider alternative therapies that are not moderate CYP3A inducers during Aqvesme treatment. If there are no alternative therapies, monitor Hb and do not exceed the maximum recommended dose of 100mg BID.
  - Avoid the coadministration of Aqvesme with sensitive CYP3A substrates that have narrow therapeutic index when coadministered with Aqvesme.
  - Avoid the 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 non-hormonal contraception during concomitant use and for 28 days after discontinuation of Aqvesme.
  - Aqvesme induces CYP2B6, CYP2C8, CYP2C9, and CYP2C19 enzymes in vitro, and may decrease systemic concentrations of drugs that are sensitive substrates of these enzymes.
    - Monitor patients for loss of therapeutic effect of sensitive substrates of these enzymes with narrow therapeutic index when coadministered with Aqvesme.
  - Aqvesme induces UGT1A1 in vitro and may decrease systemic concentrations of drugs that are UGT1A1 substrates.
    - Monitor patients for loss of therapeutic effect of UGT1A1 substrates with narrow therapeutic index when coadministered with Aqvesme.
  - Aqvesme inhibits the P-gp transporter in vitro and may increase systemic concentrations of drugs that are P-gp substrates.
    - Monitor patients for adverse reactions of P-gp substrates with narrow therapeutic index when coadministered with Aqvesme.

- **Special populations:**
  - There is no pregnancy category for this medication; however, the risk summary indicates that available data from clinical trials are not sufficient to assess for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.
    - There are clinical considerations listed.
  - The safety and efficacy of use have not been established in the pediatric population.

Conclusion

- Thalassemia's are described by a decrease in production of the alpha or beta chains that make the hemoglobin molecule, which creates an imbalance in the normal alpha to beta chain ratio (*Benz Jr and Angelucci 2026a*).
- Aqvesme is a pyruvate kinase activator indicated for the treatment of anemia in adults with alpha- or beta-thalassemia.

- Aqvesme has a box warning regarding hepatocellular injury, as it can cause serious hepatocellular injury.
  - Measure liver laboratory tests at baseline and every 4 weeks for 24 weeks and then as clinically indicated.
  - Avoid use in patients with cirrhosis and discontinue treatment if hepatic injury is suspected.
  - Due to the risk of hepatocellular injury, Aqvesme is available only through a restricted program under a REMS called the Aqvesme REMS.
- Its efficacy was assessed in patients with transfusion-dependent and non-transfusion dependent alpha- or beta-thalassemia.
  - In transfusion-dependent alpha or beta-thalassemia (the ENERGIZE-T study), efficacy was based upon transfusion reduction response. Aqvesme was significantly more effective than placebo.
  - In non-transfusion-dependent alpha- or beta-thalassemia (the ENERGIZE study), efficacy was based upon Hb response and a mean change from baseline in fatigue-related symptoms and impacts. Aqvesme was significantly more effective than placebo.
- Guidelines discuss blood transfusions as an option, while luspatercept is listed as a novel treatment.

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

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

References

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