

mitapivat (Aqvesme™)**Policy # 00962**

Original Effective Date: 05/01/2026

Current Effective Date: 05/01/2026

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Investigational or experimental services are not covered. This includes any drug, device, procedure, or service provided under the investigational arm of a clinical trial or clinical study. These services are excluded from coverage under benefits.

Note: mitapivat (Pyrukynd®)† is addressed separately in medical policy 00799.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member’s contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider mitapivat (Aqvesme™)† for the treatment of alpha- or beta- thalassemia to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for mitapivat (Aqvesme) will be considered when the following criteria are met:

- **Initial**
 - Patient has a diagnosis of alpha- or beta-thalassemia confirmed by genetic testing; AND
 - Patient does NOT have a history of homozygous or heterozygous sickle hemoglobin or hemoglobin C; AND
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
 - Patient is greater than or equal to 18 years of age; AND
 - Patient meets ONE of the following:
 - Hemoglobin (Hb) less than or equal to 10 g/dL based on an average of at least two measurements separated by at least 7 days; OR
 - Patient is considered to be transfusion dependent based on ONE of the following:
 - ❖ Patient has required at least 6 units of packed red blood cells (RBCs) over the preceding 6 months; OR
 - ❖ Patient has not had a transfusion-free period greater than 35 days in the preceding 24 weeks; AND

*(Note: These specific patient selection criteria are additional Company requirements for coverage eligibility and will be denied as not medically necessary** if not met)*

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- Aqvesme will not be used in combination with luspatercept (Reblozyl®)†; AND
- Patient has not received gene therapy for thalassemia (e.g., Casgevy™, Zynteglo®)† or bone marrow or stem cell transplant; AND
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- Patient does not have liver cirrhosis.
- **Continuation**
 - Patient has received an initial authorization for Aqvesme; AND
 - According to the prescriber, the patient has experienced clinically meaningful benefit from Aqvesme. Examples of clinical benefit include improvement in hemolytic anemia, increases in hemoglobin levels, reduction in transfusion burden, improvement in laboratory results (e.g., indirect bilirubin, lactate dehydrogenase), and/or symptomatic improvement (e.g., fatigue).
*(Note: These specific patient selection criteria are additional Company requirements for coverage eligibility and will be denied as not medically necessary** if not met).*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of mitapivat (Aqvesme) for patients with a history of sickle hemoglobin or hemoglobin C or for patients who have received gene therapy for thalassemia or bone marrow or stem cell transplant or for transfusion-independent patients who do NOT have a hemoglobin less than or equal to 10 g/dL or transfusion-dependent patients who have not required at least 6 RBC units in the previous 6 months or had a transfusion period greater than 35 days in the preceding 24 weeks to be **not medically necessary.****

Based on review of available data, the Company considers the continued use of mitapivat (Aqvesme) when the patient has not experienced a clinically meaningful benefit from treatment to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of mitapivat (Aqvesme) when patient selection criteria are not met (except those denoted above as **not medically necessary****) to be **investigational.***

Background/Overview

Aqvesme is a pyruvate kinase activator indicated for the treatment of anemia in adults with alpha- or beta-thalassemia. In patients with thalassemia, increasing pyruvate kinase activity is thought to improve energy homeostasis, RBC longevity, ineffective erythropoiesis, and hemolysis. Aqvesme contains the active ingredient, mitapivat, which should be dosed as 100 mg by mouth twice daily. Mitapivat is also available as the brand Pyrukynd which is indicated for the treatment of hemolytic anemia in adults with pyruvate kinase deficiency. The dose of mitapivat for pyruvate kinase

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deficiency is much lower with a maximum dose of 50 mg twice daily. Unlike Pyrukynd, Aqvesme carries a Black Box Warning for hepatocellular injury. It also has a Risk Evaluation and Mitigation Strategy (REMS) program requiring frequent liver monitoring.

Thalassemia is a general term for a group of congenital genetic disorders characterized by low levels of hemoglobin, decreased red blood cell (RBC) production, and anemia. Adult hemoglobin is composed of two alpha-globin and two beta-globin chains. Imbalances in these globin chains impair the body's ability to produce functional adult hemoglobin. There are two main forms of thalassemia: alpha thalassemia and beta thalassemia. Alpha thalassemia is caused by reduced or absent production of alpha-globin subunits, while beta-thalassemia is caused by reduced or absent production of beta-globin subunits. Both forms can vary significantly in severity, with some patients being asymptomatic or having mild anemia to having severe anemia with fatigue, weakness, shortness of breath, dizziness, or headaches. Complications of thalassemia can include hepatosplenomegaly, heart disease, liver disease, endocrine disease, and skeletal manifestations.

Alpha-thalassemia is caused by deletions or mutations in the *HBA1* and *HBA2* genes, with disease severity determined by how many of the four alpha-globin genes are affected. Silent carriers (one gene deleted) and individuals with alpha thalassemia minor (two genes affected) are typically asymptomatic and do not require treatment. More severe forms include hemoglobin H (HbH) disease (three genes affected), which has variable clinical severity, and Hb Bart's hydrops fetalis (four genes affected), a life-threatening fetal condition now showing improved outcomes with early intervention. Treatment needs depend on transfusion status: transfusion-dependent patients require regular transfusions every 2–5 weeks along with iron chelation therapy, while some non-transfusion-dependent patients may also need chelation. Supportive care includes splenectomy for hypersplenism, cholecystectomy for recurrent gallstones, and vigilant monitoring for cardiac and hepatic iron overload.

For disease-modifying or curative therapy, allogeneic hematopoietic stem cell transplantation (HSCT) remains the only established curative option for transfusion-dependent alpha thalassemia, though its use is limited by donor availability and risks such as graft-versus-host disease and iron-related organ toxicity. Until the approval of Aqvesme, no FDA-approved pharmacologic therapies existed for alpha thalassemia. Aqvesme now provides the first targeted treatment option, particularly relevant for patients with HbH disease who are not transplant candidates.

Beta-thalassemia results from mutations in the *HBB* gene that reduce or eliminate beta-globin production, classified as β^0 (no production), β^+ (reduced production), and β^E (reduced production with HbE variant). Disease severity varies by genotype, and both β^0/β^0 and non- β^0/β^0 patients may become transfusion-dependent. In non-transfusion-dependent beta thalassemia, treatment focuses on supportive care. Aqvesme is the only FDA-approved therapy for this population; otherwise, management includes intermittent transfusions, iron chelation, and sometimes splenectomy or cholecystectomy. Hydroxyurea is not FDA-approved but is discussed in guidelines, with 40%-70% of patients showing a hemoglobin rise greater than 1 g/dL. Large, controlled trials are still needed to clarify its role. For transfusion-dependent beta thalassemia, chronic transfusions and iron chelation remain foundational therapies. Additional options include luspatercept-aamt (Reblozyl), which can

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reduce transfusion burden but requires ongoing clinic-administered injections and carries thrombotic risk. Curative-intent approaches include matched-sibling HSCT, though eligibility is limited by donor availability and iron-related organ damage. Two FDA-approved ex-vivo gene therapies—Zynteglo and Casgevy—offer donor-independent alternatives with comparable efficacy, but different safety profiles.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Aqvesme was approved in December 2025 for the treatment of anemia in adults with alpha- or beta-thalassemia.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

Transfusion-Dependent alpha- or beta-Thalassemia

The efficacy of Aqvesme in transfusion-dependent alpha- or beta-thalassemia was evaluated in ENERGIZE-T, a multinational, randomized, double-blind, placebo-controlled clinical study of 258 adult patients. Transfusion-dependent was 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). Among the 258 patients randomized, 171 patients were randomized to receive 100 mg of Aqvesme twice daily during the 48-week double-blind period.

Efficacy was assessed based on transfusion reduction response, defined as greater than or equal to 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. In the Aqvesme group, 30.4% (n = 52) met this endpoint compared to 12.6% (n = 11) in the placebo group. This corresponds to a difference of 17.6% (95% CI 8.0, 27.2) (p = 0.0003).

Non-Transfusion-Dependent alpha- or beta-Thalassemia

The efficacy of Aqvesme in non-transfusion-dependent alpha- or beta-thalassemia was evaluated in ENERGIZE, a multinational, randomized, double-blind, placebo-controlled clinical study of 194 adult patients. Patients must have 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 less than or equal to 10 g/dL. Among the 194 patients randomized, 130 patients were randomized to receive 100 mg of Aqvesme twice daily during the 24-week double-blind period.

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Efficacy was assessed based upon Hb response, defined as a greater than or equal to 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). In the Aqvesme group, 42.3% (n = 55) met the Hb response criteria compared to 1.6% (n = 1) in the placebo group. This corresponded to an adjusted rate difference of 40.9% (95% CI 32.0, 49.8) (p < 0.0001). The mean change from baseline in the FACIT-Fatigue score in the Aqvesme group was 4.85 compared to 1.46 in the placebo group (p = 0.0026).

References

1. Aqvesme [package insert]. Agios Pharmaceuticals, Inc. Cambridge, MA. Updated December 2025.
2. Aqvesme New Drug Review. IPD Analytics. Updated February 2026.

Policy History

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04/02/2026 Medical Policy Committee review

04/10/2026 Medical Policy Implementation Committee approval. New policy.

Next Scheduled Review Date: 04/2027

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;

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- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

NOTICE: If an authorization for an ongoing course of treatment has been provided to a member and the member changes from one health plan to another health plan (e.g., a member moves from carrier A to Louisiana Blue), Louisiana Blue may honor the previous health plan’s authorization for the same service under the same type of in-network benefit for a 90-day transition period. Documentation of the authorization for the ongoing course of treatment from the previous health plan must be provided to us by the member or their provider and the services provided for the course of treatment must otherwise be a covered service under the Louisiana Blue health plan. This provision does not apply to medications covered under the plan’s pharmacy benefit.