Drug Coverage Policy

Effective Date.....6/1/2026
Coverage Policy Number.....IP0782
Policy Title.....Hematology - Aqvesme

Hematology – Aqvesme

- Aqvesme™ (mitapivat tablets – Agios)

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

OVERVIEW

Aqvesme, a pyruvate kinase activator, is indicated for the **treatment of anemia in adults with alpha- or beta-thalassemia**.[1]

Clinical Efficacy
There were two multinational, randomized, double-blind, placebo-controlled, Phase III pivotal trials that evaluated Aqvesme in patients with alpha- or beta-thalassemia.[1] ENERGIZE-T involved 258 adults with transfusion-dependent alpha- or beta thalassemia and ENERGIZE included 194 adults with non-transfusion-dependent alpha- or beta-thalassemia. Randomization in both trials was in a 2:1 ratio to Aqvesme or placebo. In ENERGIZE-T, transfusion dependence was defined as having 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. In ENERGIZE, non-transfusion dependence was defined as having had no more than five RBC units transfused during the 24-week period prior to randomization and no RBC transfusions within 8 weeks. A baseline hemoglobin level ≤ 10 g/dL was required. In ENERGIZE-T, a transfusion reduction response, defined as ≥ 50% reduction from baseline in RBC 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, occurred in 30.4% of patients given Aqvesme vs. 12.6% of patients who received placebo (P = 0.0003). In ENERGIZE, hemoglobin response, defined as a ≥ 1 g/dL increase in the average hemoglobin level from Week 12 through Week 24 compared with baseline, was 42.3% for Aqvesme vs. 1.6% with placebo (P < 0.0001).

Guidelines
The Thalassaemia International Federation (TIF) has extensive guidelines for the management of transfusion-dependent beta-thalassemia (2025),[2] non-transfusion-dependent beta-thalassemia (2023),[3] and alpha-thalassemia (2023).[4] Aqvesme is not specifically addressed post-approval, but the TIF guidelines recognized that data are promising with this agent.[2-4]

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POLICY STATEMENT
Prior Authorization is required for benefit coverage of Aqvesme. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Aqvesme as well as the monitoring required for adverse events and long-term efficacy, approval requires Aqvesme to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Aqvesme is considered medically necessary when ONE of the following is met (1 or 2):

FDA-Approved Indications

1. **Alpha-Thalassemia.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient meets ONE of the following (a or b):
       - **a)** Patient has a baseline hemoglobin level of ≤ 10.0 g/dL; OR
         Note: Baseline is prior to treatment with therapies or before red blood cell transfusions.
       - **b)** According to the prescriber, the patient requires regular red blood cell transfusions as defined by meeting BOTH of the following [(1) and (2)]:

(1) Patient has received at least 6 red blood cell units within the preceding 24 weeks; AND
(2) Patient has not had any transfusion-free period > 35 days within the preceding 24 weeks; AND

iii. The medication is prescribed by or in consultation with a hematologist; OR

B) Patient is Currently Receiving Aqvesme. Approve for 1 year if, according to the prescriber, the patient has experienced clinically meaningful benefit from Aqvesme.
Note: Examples include improvement in hemolytic anemia, increases in hemoglobin levels, a reduction in transfusion burden, improvement in laboratory results (e.g., indirect bilirubin, lactate dehydrogenase), and/or symptomatic improvement (e.g., fatigue).

2. Beta-Thalassemia. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, and v):

i. Patient is ≥ 18 years of age; AND

ii. Patient meets ONE of the following (a or b):

a) Patient has a baseline hemoglobin level of ≤ 10.0 g/dL; OR
Note: Baseline is prior to treatment with therapies or before red blood cell transfusions.

b) According to the prescriber, the patient requires regular red blood cell transfusions as defined by meeting BOTH of the following [(1) and (2)];

(1) Patient has received at least 6 red blood cell units within the preceding 24 weeks; AND

(2) Patient has not had any transfusion-free period > 35 days within the preceding 24 weeks; AND

iii. Patient is not currently receiving Reblozyl (luspatercept-aamt subcutaneous injection); AND

iv. Patient has not received a gene therapy for transfusion-dependent beta-thalassemia in the past; AND
Note: Examples include Zynteglo (betibeglogene autotemcel intravenous infusion) and Casgevy (exagamglogene autotemcel intravenous infusion).

v. The medication is prescribed by or in consultation with a hematologist; OR

B) Patient is Currently Receiving Aqvesme. Approve for 1 year if the patient meets ALL of the following (i, ii, and ii):

i. According to the prescriber, the patient has experienced clinically meaningful benefit from Aqvesme; AND
Note: Examples include improvement in hemolytic anemia, increases in hemoglobin levels, a reduction in transfusion burden, improvement in laboratory results (e.g., indirect bilirubin, lactate dehydrogenase), and symptomatic improvement (e.g., fatigue).

ii. Patient is not currently receiving Reblozyl (luspatercept-aamt subcutaneous injection); AND

iii. Patient has not received a gene therapy for transfusion-dependent beta-thalassemia in the past.
Note: Examples include Zynteglo (betibeglogene autotemcel intravenous infusion) and Casgevy (exagamglogene autotemcel intravenous infusion).

Conditions Not Covered

Aqvesme for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Pyruvate Kinase Deficiency.** Pyrukynd® (mitapivat tablets) is another mitapivat product that is indicated for the treatment of hemolytic anemia in adults with pyruvate kinase deficiency.[5] The recommended dosing differs from Aqvesme.[1,5] Unlike Aqvesme, Pyrukynd does not have a Risk Evaluation and Mitigation Strategy program.[5]

2. **Patient is Currently Receiving Pyrukynd.** Pyrukynd is another mitapivat product that is indicated for the treatment of hemolytic anemia in adults with pyruvate kinase deficiency.[5] Concomitant use is not recommended.

References

1. Aqvesme™ tablets [prescribing information]. Cambridge, MA: Agios; December 2025.
2. Taher AT, Farmakis D, Porter JB, Cappellini MD, Musallam KM, editors. Guidelines for the Management of Transfusion-Dependent β-Thalassaemia (TDT) [Internet]. 5th ed. Nicosia, Cyprus: Thalassaemia International Federation; 2025. PMID: 40367250.
3. Taher AT, Musallam KM, Cappellini MD. Guidelines for the Management of Non-Transfusion-Dependent β-Thalassaemia [Internet]. 3rd ed. Nicosia (Cyprus): Thalassaemia International Federation; 2023. PMID: 38446917.
4. Amid A, Lal A, Coates TD, Fucharoen S, editors. Guidelines for the Management of α-Thalassaemia [Internet]. Nicosia (Cyprus): Thalassaemia International Federation; 2023. PMID: 38556968.
5. Pyrukynd® tablets [prescribing information]. Cambridge, MA: Agios; December 2025.

Revision Details

Summary of Changes	Review Date	Effective Date
New policy.	4/9/2026	6/1/2026

The policy effective date is in force until updated or retired.