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Policy Number: C22822-A

Mitapivat (Aqvesme, Pyrukynd)

PRODUCTS AFFECTED

Aqvesme (mitapivat), Pyrukynd (mitapivat)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Pyruvate kinase (PK) deficiency, Alpha- or Beta-thalassemia

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. PYRUVATE KINASE (PK) DEFICIENCY (PYRUKYND ONLY):
1. Documented diagnosis of pyruvate kinase deficiency
   AND
2. Documentation diagnosis confirmed with genetic testing showing:
   a. Member has at least two mutant alleles in the PKLR (pyruvate kinase liver and red blood cell) gene, of which at least one is a missense mutation AND
   b. Member is not homozygous for the R479H mutation AND
   c. Member does not have two non-missense variants in the PKLR gene, without the presence of another missense variant
   AND
3. Documentation that in the previous 12 months, member has required at least 6 red blood cell transfusions
   AND
4. Documentation that member's baseline hemoglobin is ≤ 10 mg/dL [DOCUMENTATION REQUIRED]
   AND
5. Prescriber attests a recent review of member's current medication has been completed and prescriber has not found any interactions or will appropriately monitor for adverse reactions and hemoglobin due to the interactions.
   NOTE: Avoid use of Pyrukynd concomitantly with strong CYP3A inhibitors or inducers. When used with a moderate CYP3A inhibitor, Pyrukynd dose should not exceed 20 mg twice daily.
   AND
6. Member will receive folic acid supplementation throughout treatment with requested therapy
   AND
7. Member does not have moderate or severe hepatic dysfunction

B. ALPHA- OR BETA-THALASSEMIA (AQVESME ONLY):
1. Documented diagnosis of alpha- or beta-thalassemia (beta-thalassemia with or without alpha-globin gene mutations, HbE/beta-thalassemia, or alpha-thalassemia/HbH disease)
   AND
2. Documentation of ONE of the following:
   a. Member is transfusion dependent as evidenced by requirement of regular blood transfusions (6-20 RBC units per 24 weeks) AND Documentation of pre-treatment transfusion burden
      OR
   b. Member is not transfusion dependent (≤ 5 RBC units per 24 weeks) AND Documentation hemoglobin is ≤ 10 g/dL
   AND
3. Member will continue to receive best supportive care (RBC transfusions, iron-chelating agents, use of antibiotic, antiviral, and antifungal therapy, and/or nutritional support, as needed)
   AND
4. Prescriber attests a recent review of member's current medication has been completed and prescriber has not found any interactions or will appropriately monitor for adverse reactions and hemoglobin due to the interactions
   NOTE: Avoid use of Aqvesme concomitantly with strong CYP3A inhibitors or inducers and moderate CYP3A inhibitors.
   AND
5. Member does not have cirrhosis (Child-Pugh Clas A, B, or C)

CONTINUATION OF THERAPY:

A. PYRUVATE KINASE (PK) DEFICIENCY (PYRUKYND ONLY):

1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
   AND
2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
   AND
3. Documentation of positive clinical response as demonstrated by an increase in hemoglobin ≥ 1.5 mg/dL from baseline and/or documented reduction in transfusion burden [DOCUMENTATION REQUIRED]
   AND
4. Prescriber attests a recent review of member's current medication has been completed and prescriber has not found any interactions or will appropriately monitor for adverse reactions and hemoglobin due to the interactions.
   NOTE: Avoid use of Pyrukynd concomitantly with strong CYP3A inhibitors or inducers. When used with a moderate CYP3A inhibitor, Pyrukynd dose should not exceed 20 mg twice daily.

B. ALPHA- OR BETA-THALASSEMIA (AQVESME ONLY):

1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
   AND
2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
   AND
3. FOR TRANSFUSION DEPENDENT ANEMIA: Documentation that member has had a decrease in RBC transfusion burden from pre-treatment baseline
   NOTE: 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).
   AND
4. FOR NON-TRANSFUSION DEPENDENT ANEMIA: Documentation of improvement in hemoglobin
   NOTE: 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).
   AND
5. Prescriber attests a recent review of member's current medication has been completed and prescriber has not found any interactions or will appropriately monitor for adverse reactions and hemoglobin due to the interactions
   NOTE: Avoid use of Aqvesme concomitantly with strong CYP3A inhibitors or inducers and moderate CYP3A inhibitors.

DURATION OF APPROVAL:

Initial authorization: 6 months, Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:
Prescribed by or in consultation with a board-certified hematologist. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests.]

AGE RESTRICTIONS:
18 years of age and older

QUANTITY:
Pyrukynd:
One (1) 28-day pack per month
One Taper Pack, as needed for interruption in treatment or discontinuation

Maximum Quantity Limits – 50 mg twice daily
If Pyrukynd is used with a moderate CYP3A inducer (e.g., efavirenz) and therapy with the inducer has no alternative - 100 mg twice daily

Aqvesme: 100 mg twice daily

PLACE OF ADMINISTRATION:
The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Pyruvate Kinase Activators

FDA-APPROVED USES:
Pyrukynd is indicated for the treatment of hemolytic anemia in adults with pyruvate kinase (PK) deficiency.
Aqvesme is indicated for the treatment of anemia in adults with alpha- or beta-thalassemia.

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

Dose Titration Schedule for initiation of treatment with Pyrukynd:

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.

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Pyruvate kinase (PK) deficiency is a rare hereditary disorder which affects red blood cell (RBC) glycolysis. Pyruvate kinase catalyzes the final step in glycolysis, which is needed to produce adenosine triphosphate (ATP) in the red blood cell. Without ATP, the RBCs breakdown prematurely. Alterations in the PKLR gene are inherited in an autosomal recessive manner and result in a deficiency in the pyruvate kinase enzyme. Due to this deficiency RBCs last days to weeks, rather than the typical average of 120 days. This results in a lifelong, chronic hemolytic anemia. The estimated disease prevalence is 1 per 20,000 in the Caucasian population. There is a higher prevalence in the Pennsylvania Amish community due to the founder effect.

The signs and symptoms of pyruvate kinase deficiency can include anemia, fatigue, exercise intolerance, jaundice, memory loss, and difficulty concentrating. Additional complications are also observed in individuals with PK deficiency, including iron overload, gallstones, bone fracture/osteoporosis, and spleen enlargement. Management of PK deficiency is supportive and includes RBC transfusions, splenectomy, cholecystectomy, and iron chelation therapy.

Pyrukynd (mitapivat) is an oral small molecule allosteric activator of the pyruvate kinase enzyme. Mitapivat binds to and activate the PK enzyme, increasing ATP production in the RBC. Mitapivat was studied in two clinical trials: ACTIVATE (NCT03548220) and ACTIVATE-T (NCT03559699). ACTIVATE was a phase 3, randomized, double-blind placebo-controlled trial in 80 patients with pyruvate kinase deficiency (PKD), who were not regularly receiving blood transfusion. The study was divided into two segments. The first was a dose optimization period in which the dose was started at 5 mg twice daily followed by sequential dose increases to 20 mg twice daily and 50 mg twice daily, depending upon tolerance. The second part was a fixed dose period, in which the participants received their optimized dose. Participants were 18 years and older, with a confirmed diagnosis of PKD documented by the presence of at least 2 mutant alleles in the PKLR gene, of which at least 1 is a missense mutation. Participants were excluded if they were homozygous for the R479H mutation or have 2 non-missense mutations, without the presence of another missense mutation, in the PKLR gene. Baseline hemoglobin concentration for all participants was requires to be less than or equal to 10.0 g/dL regardless of gender. Participants could have received no more than 4 transfusions in the 12 months prior to the study and no transfusion sin the 3 months prior to the study. Hemoglobin response was defined as a ≥1.5 g/dL increase in Hb from baseline sustained at two or more scheduled assessments (Weeks 16, 20, and 24) during the fixed-dose period without transfusions. Hemoglobin response was achieved in 16 participants (40%, n=40) in the Pyrukynd group and 0 participants in the placebo group (n=40), which was a statistically significant difference

(p<0.0001). ACTIVATE-T evaluated the efficacy of mitapivant in participants that received regular transfusions. This trial was a multinational single arm trial in 27 adults with PKD. Participants were required to have received a minimum of 6 transfusion episodes in the 52-week period prior to study consent. Participants were required to have a confirmed diagnosis of PKD documented by the presence of at least 2 mutant alleles in the PKLR gene, of which at least 1 is a missense mutation. Participants were excluded if they were homozygous for the R479H mutation or have 2 non-missense mutations, without the presence of another missense mutation, in the PKLR gene. Participants (n=27) had a median of 9 transfusion episodes prior to the study, with a median of 7 RBC units transfused standardized to 24 weeks. Efficacy was defined as a ≥ 33% reduction in RBC units transfused during the study period compared to the participants baseline.
Nine participants (33%) achieved the defined transfusion response (95% CI 17,54) and six participants (22%) were transfusion free (95% CI 9, 42).

In the ACTIVATE trial, the most In the ACTIVATE trial, the most common adverse reactions including laboratory abnormalities (≥ 10%) in patients with PK deficiency were estrone decreased (males), increased urate, back pain, estradiol decreased (males), and arthralgia. The adverse reactions reported in the population of patients who were regularly transfused (ACTIVATE-T) were consistent with that seen in ACTIVATE.

Beta thalassemia is part of a group of rare, inherited blood disorders caused by a genetic defect in hemoglobin, characterized by reduced levels of functional hemoglobin. Hemoglobin is an iron-containing protein in red blood cells that carries oxygen to cells throughout the body. Low levels of hemoglobin lead to a lack of oxygen in many parts of the body and anemia, which can cause pale skin, weakness, fatigue, and more serious complications. Organ damage (e.g., renal disease, cardiomyopathy, diabetes) can result. There are three main forms of beta thalassemia – minor, intermedia, and major, terms which indicate the severity of the disease. Individuals with the minor form, also known as beta thalassemia trait, may experience minor anemia, but they usually do not have symptoms and often are unaware that they have the condition. Individuals with the intermedia form experience a wide range of symptoms, and the severity falls in the broad range between the major and minor forms. Beta thalassemia major, also known as Cooley's anemia, is the severest form of the disorder. Individuals with beta thalassemia major often require regular blood transfusions (about every 2–4 weeks) and lifelong, ongoing medical care. These Individuals are at risk for iron overload, or too much iron in the body, due to the chronic blood transfusions and require medicines to remove extra iron from their bodies (called chelation). People with beta thalassemia are also at an increased risk of developing blood clots. Hematologists treat patients with beta thalassemia. There are CDC funded Thalassemia Treatment Centers throughout the country.

The efficacy and safety of Aqvesme for anemia in thalassemia were evaluated in two multinational, randomized, double-blind, placebo-controlled clinical studies. The ENERGIZE-T study evaluated 258 adults with transfusion-dependent thalassemia, with 171 adults receiving Aqvesme and 87 receiving placebo. Efficacy was based upon transfusion reduction response, defined as greater than 50% reduction in the number of red blood cell units transfused with a reduction of at least two units in any consecutive 12-week period between the baseline visit and Week 48. A higher proportion of patients taking Aqvesme achieved a transfusion reduction response (30%) compared with the placebo group (13%).
A second trial, the ENERGIZE study, evaluated Aqvesme in 194 adults with non-transfusion-dependent thalassemia over 24 weeks, with 130 adults receiving Aqvesme daily and 64 receiving placebo. Efficacy was based upon hemoglobin response (a measure of the improvement in anemia), defined as a ≥ 1 g/dL increase from baseline in mean hemoglobin concentration at Week 24. A higher

proportion of patients taking Aqvesme achieved a hemoglobin response (42%) compared with the placebo group (2%).
Another efficacy endpoint in the ENERGIZE study assessed the mean change from baseline in fatigue-related symptoms and impacts using a patient-reported outcome instrument, the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue). The FACIT-F total score has a range of 0 to 52, with higher scores indicating less fatigue. At baseline, the mean FACIT-F score was approximately 36. Patients treated with Aqvesme had a mean increase in the FACIT-F total score of 4.9 compared to a mean increase of 1.5 in patients taking placebo.
Aqvesme is only available through a restricted program called the Aqvesme Risk Evaluation and Mitigation Strategies (REMS) because of the risk of liver toxicity observed in the clinical trials.
The most common side effects of Aqvesme are headache and insomnia. More safety information is available in the prescribing information.

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.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of mitapivat are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to mitapivat include: avoid concomitant use with strong CYP3A inhibitors and inducers, avoid concomitant use with sensitive CYP3A, CYP2B6, CYP2C substrates including hormonal contraceptives, that have a narrow therapeutic index. Avoid use of Pyrukynd in patients with moderate or severe hepatic impairment. Avoid use of Aqvesme in patients with cirrhosis (Child-Pugh Class A, B or C).

OTHER SPECIAL CONSIDERATIONS:
Aqvesme (mitapivat) has a Black Box Warning for hepatocellular injury and is available only through a restricted REMS program.

Mitapivat is taken with or without food and is swallowed whole. Tablets are not to be split, crushed, chewed, or dissolved. Blister wallets should be stored in the original carton until use.

Pyrukynd (mitapivat) should be started at 5 mg twice daily for the first 4 weeks. The dose may then be increased to 20 mg twice daily for the next 4 weeks (weeks 5 through 8), if the member's hemoglobin is below normal or the member has required a transfusion within the last 8 weeks. The dose may be increased to 50 mg twice daily (maximum dose), if the member's hemoglobin is below normal or the member has required a transfusion within the last 8 weeks. If the

member achieves a hemoglobin above more and has not required a transfusion in the previous 8 weeks, the current dose (5 mg, 20 mg or 50 mg twice daily) should be maintained.

To avoid the risk of acute hemolysis, Pyrukynd (mitapivat) should not be abruptly interrupted or discontinued. The dose should be tapered over 7 to 14 days, dependent upon the current dose.

Dose Taper Schedule:

Current Dose	Day 1-7	Day 8-14	Day 15
5 mg twice daily	5 mg once daily	Discontinue	
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

Special Populations:
Safety and efficacy of Pyrukynd (mitapivat) has not been established in pediatric patients.
Mitapivat undergoes extensive hepatic metabolism. Moderate and severe hepatic impairment is expected to increase the systemic exposure, therefore use should be avoided in this population.

CODING/BILLING INFORMATION

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.*

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Aqvesme TABS 100MG
Pyrukynd TABS 5MG
Pyrukynd TABS 20MG
Pyrukynd TABS 50MG
Pyrukynd Taper Pack TBPK 5MG
Pyrukynd Taper Pack TBPK 7 x 20 MG &7 x 5 MG
Pyrukynd Taper Pack TBPK 7 x 50 MG &7 x 20 MG

REFERENCES

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10. Taher, A. T., Farmakis, D., Porter, J. B., Cappellini, M. D., & Musallam, K. M. (2025). Guidelines for the Management of Transfusion-Dependent β-Thalassaemia (TDT) 5th Edition. Thalassaemia International Federation.

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Diagnosis Required Medical Information Continuation of Therapy Quantity FDA-Approved Uses Background Contraindications/Exclusions/Discontinuation Other Special Considerations Available Dosage Forms References	Q1 2026
REVISION- Notable revisions: Continuation of Therapy References	Q1 2025
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Quantity	Q1 2024
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Contraindications/Exclusions/Discontinuation	Q1 2023

NEW CRITERIA CREATION	Q2 2022