Original Effective Date: 09/06/2026
Current Effective Date: 09/06/2026
Last P&T Approval/Version: 07/29/2026
Next Review Due By: 07/2027
Policy Number: C30839-A

Kygevvi (doxecitine and doxribtimine)

PRODUCTS AFFECTED

Kygevvi (doxecitine and doxribtimine)

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:
Thymidine Kinase 2 Deficiency

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. This clinical policy will be reviewed along with state and federal requirements, the benefit being administered and formulary preferencing. 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. 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. The Pharmacy and Therapeutics Committee has determined that biosimilars may be preferred.

A. THYMIDINE KINASE 2 DEFICIENCY:
   1. Documented diagnosis of thymidine kinase 2 deficiency (TK2d)
      AND

2. Documentation diagnosis was confirmed by genetic testing that shows mutations in the TK2 gene
   AND
3. Documentation of symptom onset (e.g., limb weakness, facial paralysis, breathing difficulties, hypotonia, feeding difficulties, failure to thrive) at or before 12 years of age
   AND
4. Documentation of prescriber baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal (i.e., 6-minute walk test, fatigue assessment, activities of daily living, muscle strength assessment, cardiac evaluation, pulmonary function test)
   NOTE: The same assessment should be used in the follow-up evaluation for reauthorization for continuation of therapy. If the initial assessment tool is not appropriate (i.e., due to change in member's status or age range of the assessment), submit the rationale for change in assessment tool.

CONTINUATION OF THERAPY:

A. THYMIDINE KINASE 2 DEFICIENCY:
   1. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
      AND
   2. Documentation of positive or stable clinical response as demonstrated by low disease activity and/or improvements in the condition's signs and symptoms (i.e., 6-minute walk test, fatigue assessment, activities of daily living, muscle strength assessment, cardiac evaluation, pulmonary function test)
      NOTE: The same assessment should be what was provided on initial review. If the initial assessment tool is not appropriate (i.e., due to change in member's status or age range of the assessment), submit the rationale for change in assessment tool.

DURATION OF APPROVAL:

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

PRESCRIBER REQUIREMENTS:

Prescribed by or in consultation with a board-certified neurologist or specialist experienced in managing mitochondrial myopathies [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

1 month of age and older

QUANTITY:

Starting Dose: 260 mg/kg/day (consisting of 130 mg doxecitine and 130 mg doxribtimine)
Intermediate Dose: 520 mg/kg/day (consisting of 260 mg doxecitine and 260 mg doxribtimine)
Maintenance Dose: 800 mg/kg/day (consisting of 400 mg doxecitine and 400 mg doxribtimine)

The recommended dose of Kygevvi is based on actual body weight. Titrate to the next dosage level based on tolerability after a minimum of 2 weeks at the current dosage level.

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:
Metabolic Modifier Combinations

FDA-APPROVED USES:
Indicated for the treatment of thymidine kinase 2 deficiency (TK2d) in adults and pediatric patients with an age of symptom onset on or before 12 years.

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Thymidine kinase 2 deficiency (TK2d) is a rare, autosomal recessive mitochondrial DNA (mtDNA) depletion syndrome caused by pathogenic variants in the TK2 gene. This gene encodes a mitochondrial enzyme involved in the salvage pathway of pyrimidine nucleosides, essential for maintaining adequate mtDNA replication in post-mitotic tissues such as skeletal muscle. Deficiency leads to reduced mtDNA copy number, impaired oxidative phosphorylation, and progressive myopathic disease.

Management of TK2d is primarily supportive, focusing on respiratory care and symptom control of muscle weakness. TK2d symptoms overlap with other neuromuscular disorders (e.g. Pompe disease, muscular dystrophy, and spinal muscular atrophy), which often leads to delayed diagnosis. Patients with mitochondrial diseases such as TK2d typically wait 8–10 years for an accurate diagnosis.

TK2d has a broad clinical spectrum, typically categorized by age of onset:
1. Infantile-Onset (≤1 year of age)
   - Severe, rapidly progressive myopathy
   - Generalized hypotonia (“floppy infant”)
   - Feeding difficulties, failure to thrive
   - Respiratory insufficiency (often ventilator dependence)
   - Early mortality (often within first few years without treatment)

2. Childhood-Onset (2–12 years of age)
   - Proximal muscle weakness
   - Delayed motor milestones or regression
   - Progressive respiratory involvement
   - Scoliosis may develop
   - Variable rate of progression

3. Late-Onset / Adult-Onset (>12 years of age)
   - Slowly progressive limb-girdle muscle weakness
   - Exercise intolerance
   - Ptosis or ophthalmoparesis (less common than other mitochondrial disorders)
   - Respiratory muscle involvement in advanced disease

Given the similarities with other neuromuscular and mitochondrial myopathies, genetic testing inclusive of the TK2 gene is the most accurate method for confirming diagnosis. However, patients are often initially assessed with muscle enzyme tests, electromyography, magnetic resonance imaging (MRI), and muscle biopsy prior to receiving a definitive diagnosis.

Kygevvi is the first FDA-approved therapy for TK2d. It is a combination of doxecitine and doxribtimine, two pyrimidine nucleosides (PYds). PYds are naturally occurring compounds that serve as building blocks for mtDNA. Kygevvi, a fixed-dose oral formulation of two synthetic PYds (doxecitine and doxribtimine) replaces these missing substrates in patients with TK2d, thereby restoring mtDNA maintenance and energy production.

The efficacy of Kygevvi for the treatment of patients with TK2d, with an age of symptom onset on or before 12 years of age, was established based on data from one Phase 2 clinical study (Trial 1), two retrospective chart review studies (Study 1, Study 2), and an expanded access program. The survival in treated patients was compared with survival in an untreated external control group comprised of untreated patients from published literature and Study 2.

Trial 1 (NCT03845712) is a prospective, open-label, single-arm study in 47 patients with genetically confirmed TK2d previously treated with pyrimidine nucleosides. Thirty-eight of these 47 patients have an age of TK2d symptom onset ≤12 years; none of the 38 patients discontinued treatment. The initial oral dose of Kygevvi was matched to the patient's pyrimidine nucleoside dose of 260-800 mg/kg/day upon entering the study in patients with an age of TK2d symptom onset ≤ 12 years, and dosage was titrated, as needed, over a maximum of 4 weeks to the maintenance dose of 800 mg/kg/day.

Study 1 (NCT03701568) was a retrospective chart review study in 38 patients with genetically confirmed TK2d treated with pyrimidine nucleosides. Twenty-nine of these patients had an age of TK2d symptom onset ≤12 years; none of the 29 patients discontinued treatment. Thirty-five of these 38 patients were later enrolled in Trial 1 to receive treatment with Kygevvi and one was later enrolled in Study 2. Kygevvi was not administered in Study 1. Patients enrolled in Study 1 were receiving pyrimidine nucleoside treatment at doses 160-800 mg/kg/day.

Study 2 (NCT05017818) was a retrospective chart review study in 61 patients with genetically confirmed TK2d (43 untreated patients and 18 patients treated with pyrimidine nucleoside therapy). Nine of these 61 patients were also included in the expanded access program and 1 patient was included in Study 1. Twenty-seven of the 43 untreated patients had an age of TK2d symptom onset ≤12 years, and 13 of the 18 treated patients had an age of TK2d symptom onset ≤12 years. Twenty-two untreated patients were included in the untreated external control group used to evaluate survival. Of the 18 patients treated, 6 (33%) discontinued treatment due to an adverse reaction. Kygevvi was not administered in Study 2. Patients enrolled in Study 2 were receiving pyrimidine nucleoside treatment at doses 200-1200 mg/kg/day.

Expanded Access Program

The expanded access program data included 43 patients receiving Kygevvi; 9 patients were included in Study 2.

Efficacy Results

A total of 82 patients with genetically confirmed TK2d and the age of symptom onset ≤12 years were treated with Kygevvi or pyrimidine nucleosides. Efficacy was assessed by comparing overall survival in the treated patients to an external control group of untreated patients matched to treated patients using age of TK2d symptom onset (≤ 2 years or >2 to ≤ 12 years). A total of 78 matched pairs were identified.

For the 78 treated patients included in the survival analysis, the median age of TK2d symptom onset was 1.5 years (range: 0.01 to 12 years). The median duration of treatment was 4 years (range: 1 day to 12 years) and the median dose received was 762 mg/kg/day (range: 260 to 800 mg/kg/day).

Treatment reduced the overall risk of death from treatment start by approximately 86%.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Kygevvi (doxecitine and doxribtimine) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Kygevvi (doxecitine and doxribtimine) include: no labeled contraindications.

Exclusions/Discontinuation:

Elevated Liver Transaminase Levels

Obtain baseline liver transaminase (ALT, AST) and total bilirubin levels prior to treatment initiation with Kygevvi. If signs or symptoms consistent with liver injury are observed, interrupt treatment. Consider permanently discontinuing Kygevvi if signs/symptoms consistent with liver injury persist or worsen. Monitor patients yearly and as clinically indicated.

Gastrointestinal Adverse Reactions

Reduce Kygevvi dosage or interrupt treatment based on severity of diarrhea and/or vomiting. If persistent severe diarrhea and/or vomiting occurs, consider discontinuing Kygevvi permanently.

OTHER SPECIAL CONSIDERATIONS:

Kygevvi (doxecitine and doxribtimine) powder must be reconstituted with water prior to administration. Preparation of Kygevvi with a liquid other than water has not been studied clinically and is not recommended.

Use the administration kit (provided separately) to prepare and administer the prescribed dose. Household devices such as measuring cups or spoons are not adequate measuring devices. Kygevvi should be prepared and administered by adults only.

Kygevvi may be administered orally or with a feeding tube. Administer Kygevvi in 3 equally divided doses approximately 6 hours apart (plus or minus 2 hours) with food. If a dose is missed, take the missed dose as soon as possible but do not take within 2 hours of the next scheduled dose. In that case, skip the missed dose and resume the regular schedule. A double dose should not be taken to make up for the missed dose.

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:

Kygevvi PACK 2-2GM

REFERENCES

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2. An open-label study of continuation treatment with combination pyrimidine nucleosides in patients with TK2 deficiency (continuation). https://clinicaltrials.gov/study/NCT03845712 (Accessed on December 09, 2025).
3. A retrospective study of subjects with thymidine kinase 2 deficiency. https://clinicaltrials.gov/study/NCT05017818 (Accessed on December 09, 2025).
4. A RETROspective study of patients with TK2d (RETRO). https://clinicaltrials.gov/study/NCT03701568 (Accessed on December 09, 2025).
5. UCB BIOSCIENCES, Inc. (2025, September) Doxecitine and doxribtimine—Expanded access (ClinicalTrials.gov Identifier: NCT06590493). ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT06590493
6. Domínguez-González, C., Chiang, C., Colson, A. O., Rebollo Mesa, I., Baixauli, E., Quan, J., VanMeter, S., & Hirano, M. (2025). Pyrimidine nucleos(t)ide therapy in patients with thymidine kinase 2 deficiency: A multicenter retrospective chart review study. Neurology, 105(6), e213908. https://doi.org/10.1212/WNL.0000000000213908
7. Thymidine Kinase 2 Deficiency. (2025, March 4). National Organization for Rare Disorders. https://rarediseases.org/rare-diseases/thymidine-kinase-2-deficiency/
8. Scaglia, F., Hirano, M., Garone, C., Haas, R., Paradas, C., Beller, C., Chiang, C., Colson, A.-O., VanMeter, S., & Domínguez-González, C. (2025, March). Survival and functional outcomes in patients with thymidine kinase 2 deficiency aged >12 years at symptom onset who received pyrimidine nucleos(t)ides [Conference presentation]. Muscular Dystrophy Association (MDA) Clinical & Scientific Conference, Dallas, TX, United States. Available at: https://www.ucbcompass.com/sites/default/files/2025-05/MDA%202025_ISS-ISE_above%2012%20years%20poster_P256_FINAL.pdf

SUMMARY OF REVIEW/REVISIONS	DATE
NEW CRITERIA CREATION	Q3 2026