

doxecitine and doxribtimine (KygevvTM)

Policy # 00980

Original Effective Date: 08/01/2026

Current Effective Date: 08/01/2026

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.

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 doxecitine and doxribtimine (KygevvTM)[‡] 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 to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility for doxecitine and doxribtimine (Kygevv) will be considered when the following criteria are met:

- Patient has a diagnosis of thymidine kinase 2 deficiency (TK2d); AND
- Diagnosis has been confirmed by genetic testing demonstrating biallelic pathogenic or likely pathogenic variants in the *TK2* gene; AND
- Patient experienced onset of symptoms attributable to TK2d at 12 years of age or younger.

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 doxecitine and doxribtimine (Kygevv) when the patient selection criteria are not met to be **investigational**.*

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Background/Overview

Kygevvi (doxecitine and doxribtimine) is an oral combination of two pyrimidine nucleosides approved for the treatment of thymidine kinase 2 deficiency (TK2d) in adults and pediatric patients with symptom onset on or before 12 years of age. Kygevvi received Breakthrough Therapy, Orphan Drug, Rare Pediatric Disease, and Priority Review designations and is the first FDA-approved treatment for TK2d. Kygevvi is supplied as a powder for oral solution in single-use packets containing 2 g of doxecitine and 2 g of doxribtimine (4 g total powder). The medication is reconstituted with water and administered orally or through compatible feeding tubes using the manufacturer-provided ZX2000 administration kit. Dosing is weight-based and administered with food in three equally divided doses approximately 6 hours apart. Recommended dosage levels include a starting dosage of 260 mg/kg/day (130 mg/kg/day of each component), an intermediate dosage of 520 mg/kg/day (260 mg/kg/day of each component), and a maintenance dosage of 800 mg/kg/day (400 mg/kg/day of each component). Patients may be titrated to the next dosage level after a minimum of 2 weeks at the current dosage based on tolerability. Treatment should be interrupted if signs or symptoms consistent with liver injury are observed or if there is severe diarrhea and/or vomiting.

TK2d is an ultra-rare, progressive, and often life-threatening mitochondrial myopathy caused by autosomal recessive pathogenic variants in the *TK2* gene. The disorder disrupts normal maintenance of mitochondrial DNA, resulting in impaired cellular energy production and progressive muscle dysfunction. Clinical manifestations vary according to age of onset but commonly include worsening muscle weakness, respiratory impairment, feeding or swallowing difficulties, impaired motor development, and reduced physical function. Disease severity is generally related to age at symptom onset. Infantile-onset disease (less than 1 year of age) is typically the most severe and rapidly progressive form, childhood-onset disease (> 1 to 12 years of age) demonstrates intermediate severity, and late-onset disease (> 12 years of age) is generally more slowly progressive but remains associated with substantial morbidity and mortality. Respiratory failure is a leading cause of death across disease subtypes. The estimated prevalence of TK2d is approximately 1.64 cases per 1,000,000 individuals, corresponding to an estimated 550 affected individuals in the United States. Diagnosis is confirmed by genetic testing demonstrating biallelic pathogenic or likely pathogenic variants in the *TK2* gene.

Doxecitine and doxribtimine are synthetic pyrimidine nucleosides intended to restore mitochondrial DNA copy number by providing deoxycytidine and deoxythymidine substrates for incorporation into mitochondrial DNA. This nucleoside replacement approach helps overcome the biochemical defect associated with TK2 deficiency and supports mitochondrial DNA maintenance and cellular energy production. There are currently no other FDA-approved therapies for TK2d. Prior to the approval of Kygevvi, management consisted primarily of supportive care measures, including respiratory support, nutritional and feeding interventions, physical therapy, and management of disease-related complications.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Kygevvi was approved in November 2025 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.

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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.

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 was 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 had 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 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 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 treated patients, 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.

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

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

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approximately 86% (95% CI: 61%, 96%). The restricted mean survival time at 4-, 6-, and 10-years post-treatment was consistently higher in the treated group (3.8 years, 5.8 years, and 9.6 years, respectively) vs. the untreated group (2.6 years, 3.7 years, and 5.7 years, respectively). Functional benefits were also reported. Following treatment, only 21.7% of patients experienced loss of at least one motor milestone compared with 83.7% prior to treatment, while 75% regained at least one previously lost milestone compared with 4.9% before treatment. A reduced reliance on ventilatory assistance and feeding support was also observed.

References

1. Kygevvi [package insert]. UCB, Inc. Smyrna, Georgia. Updated November 2025.
2. Kygevvi Drug Evaluation. Express Scripts. Updated December 2025.
3. New Drug Review: Kygevvi (doxecitine and doxribtimine). IPD Analytics. Updated November 2025.

Policy History

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07/21/2026 Pre Pharmacy & Therapeutics Committee review

07/22/2026 Pharmacy & Therapeutics Committee review approval. New policy.

Next Scheduled Review Date: 07/2027

*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.