Clinical Policy: Doxecitine and Doxribtimine (Kygevvi)

Reference Number: CP.PHAR.738
Effective Date: 11.03.25
Last Review Date: 02.26
Line of Business: Commercial, HIM, Medicaid Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Doxecitine and doxribtimine (Kygevvi®) is a combination pyrimidine nucleoside therapy.

FDA Approved Indication(s)

Kygevvi is 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.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Kygevvi is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Thymidine Kinase 2 Deficiency (must meet all)**:**

1. Diagnosis of TK2d as evidenced by a mutation in the thymidine kinase 2 (TK2) gene;
2. Prescribed by or in consultation with a neurologist or metabolic disease specialist;
3. Age of symptom onset ≤ 12 years (e.g., proximal muscle weakness, respiratory weakness, facial diplegia; *see Appendix D*);
4. Documentation of member's current weight in kg;
5. Dose does not exceed doxecitine 400 mg/kg and doxribtimine 400 mg/kg per day (*see Appendix E for the recommended number of packets per day based on total daily dose*).

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business:

CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Thymidine Kinase 2 Deficiency (must meet all)**:**

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B)*;
2. Member is responding positively to therapy;
3. Documentation of member's current weight in kg;
4. If request is for a dose increase, new dose does not exceed doxecitine 400 mg/kg and doxribtimine 400 mg/kg per day (*see Appendix E for the recommended number of packets per day based on total daily dose*).

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
TK2d: thymidine kinase 2 deficiency

Appendix B: Therapeutic Alternatives
Not applicable

Appendix C: Contraindications/Boxed Warnings
None reported

Appendix D: General Information

- Clinical symptoms of TK2d:
  - Proximal muscle weakness (muscle weakness affecting the muscles of the trunk, shoulders, and thighs)
  - Respiratory weakness (including mechanical ventilation or continuous non-invasive ventilation)
  - Loss in motor functions (holding head upright, sitting, standing, walking, climbing, running)
  - Facial diplegia
  - Ptosis (droopy eyelids)
  - Seizures
  - Encephalopathy
  - Dysphagia
  - Cognitive dysfunction or decline
  - Multiple bone fractures

Appendix E: Number of Packets Based on Total Daily Dose per Prescribing Information

Total Daily Dose (mg/day)	Total Number of Kygevvi Packets for Reconstitution
750 – 4,049	1
4,050 – 8,249	2
8,250 – 12,749	3
12,750 – 17,249	4
17,250 – 21,749	5
21,750 – 24,749	6
24,750 – 29,249	7
29,250 – 33,749	8
33,750 – 38,249	9
38,250 – 42,749	10
42,750 – 47,249	11
47,250 – 51,749	12
51,750 – 54,749	13
54,750 – 59,249	14
59,250 – 63,749	15
63,750 – 68,249	16

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
TK2d	Kygevvi is administered PO in 3 equally divided doses: • Starting: 260 mg/kg/day (consisting of 130 mg doxecitine and 130 mg doxribtimine) • Intermediate: 520 mg/kg/day (consisting of 260 mg doxecitine and 260 mg doxribtimine) • Maintenance: 800 mg/kg/day (consisting of 400 mg doxecitine and 400 mg doxribtimine) Titrate to the next dosage level based on tolerability after a minimum of 2 weeks at the current dosage level	800 mg/kg/day

VI. Product Availability

Powder for oral solution: 2 g doxecitine and 2 g doxribtimine

VII. References

1. Kygevvi Prescribing Information. Smyrna, GA: UCB, Inc.; November 2025. Available at: https://www.ucb-usa.com/kygevvi-prescribing-information.pdf. Accessed November 5, 2025.
2. ClinicalTrials.gov. An open-label study of continuation treatment with combination pyrimidine nucleosides in patients with TK2 deficiency (Continuation). Available at: https://www.clinicaltrials.gov/study/NCT03845712. Accessed November 5, 2025.
3. ClinicalTrials.gov. A retrospective study of subjects with thymidine kinase 2 deficiency. Available at: https://clinicaltrials.gov/study/NCT05017818. Accessed November 5, 2025.
4. ClinicalTrials.gov. A RETROspective study of patients with TK2d (RETRO). Available at: https://clinicaltrials.gov/study/NCT03701568. Accessed November 5, 2025.
5. Berardo A, Domínguez-González C, Engelstad K, et al. Advances in thymidine kinase 2 deficiency: Clinical aspects, translational progress, and emerging therapies. J Neuromuscul Dis. 2022;9(2):225-235. doi: 10.3233/JND-210786. PMID: 35094997; PMCID: PMC9028656.
6. Garone C, Taylor RW, Nascimento A, et al. Retrospective natural history of thymidine kinase 2 deficiency. J Med Genet. 2018 Aug;55(8):515-521. doi: 10.1136/jmedgenet-2017-105012.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created pre-emptively	06.03.25	08.25
Drug is now FDA approved – criteria updated per FDA labeling; extended initial approval duration from 6 to 12 months for this maintenance medication for a chronic condition; removed specific measures of positive response; references reviewed and updated.	12.02.25	02.26

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.