New Drug Overview

Kygevvi (doxecitine and doxribtimine)
PDL Category: Immunological Agents

Introduction

Disease Background:

- Metabolic myopathies are described as a group of genetic disorders that are rare and consists of defects in cellular energy metabolism, resulting in muscle disease (*Atwal and Barron 2026*).
  - They include a wide-range of conditions with heterogenous appearance that spans from severe systemic disease resulting in infant death to adult-onset disease with mild, exertional cramps.
  - Metabolic myopathies can be categorized into 3 major types, including glycogen myopathies, lipid myopathies, and mitochondrial myopathies. These all have common clinical features.
    - The mitochondrial myopathies are a heterogenous collection of inherited disorders described as defects in mitochondrial structure or function that results in fatigue of muscles.
      - Mitochondria are organelles that generate energy for cellular processes. Furthermore, they are now involved in several facets of health and disease, such as cancer, aging, cardiovascular disorder, and nervous system disorders (*O'Ferrall 2026*).
      - One type of mitochondrial myopathy is thymidine kinase 2 (TK2) defects (*Atwal and Barron 2026*).
- Thymidine kinase 2 deficiency (TK2d) is caused by pathogenic variants in the nuclear thymidine kinase 2 (TK2) gene. The effect is depletion and numerous deletions of mitochondrial DNA (*O'Ferrall 2026*).
  - Clinically, TK2d displays as a progressive mitochondrial myopathy that generally starts in childhood.
    - Data suggest that infantile-onset (age ≤1 year) myopathy with a median survival from onset of one year and childhood-onset (age 2 to 12 years) myopathy with median survival from onset of ≥13 years were the most frequent phenotypes, while late-onset (age >12 years) myopathy with a median survival from onset of 23 years is associated with mild limb weakness.
  - Symptoms may include muscle weakness, facial diplegia, ptosis, dysphagia, or dysarthria, while less common symptoms may include seizure, encephalopathy, cognitive impairment, nephropathy, and hearing loss, among others.
- Kygevvi was FDA approved in 2025.

Pharmacology/Usage

- Kygevvi (doxecitine and doxribtimine) is a combination of two pyrimidine nucleosides.
  - Administration is intended to incorporate the pyrimidine nucleosides, deoxycytidine and deoxythymidine, into skeletal muscle mitochondrial deoxyribonucleic acid (DNA). This action restores mitochondrial DNA copy number in TK2d mutant mice.

Indications

Table 1. Food and Drug Administration Approved Indications

Indication	Kygevvi (doxecitine & doxribtimine)
• 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.	√

(Prescribing information: Kygevvi 2025)

- Information on indications, mechanism of action, pharmacokinetics, dosing, safety, and clinical efficacy summary has been obtained from the prescribing information for the individual products, except where noted otherwise.

Dosing and administration

Table 2. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Kygevvi (doxecitine & doxribtimine)	Powder for Oral Solution: 2g doxecitine and 2g doxribtimine in a single use packet.	PO	Dosage based on patient's weight, and titrate to the next dosage level based on tolerability after a minimum of 2 weeks at the current dosage level. Start: 260mg/kg/day (consisting of 130mg doxecitine and 130mg doxribtimine). Intermediate: 520mg/kg/day (consisting of 260mg doxecitine and 260mg doxribtimine). Maintenance: 800mg/kg/day (consisting of 400mg doxecitine and 400mg doxribtimine). -Administer in 3 equally divided doses about 6 hours apart (plus or minus 2 hours) with food.	• Obtain baseline liver transaminase (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) and total bilirubin levels in patients prior to treatment initiation with Kygevvi. • After calculating the daily dose, refer to the table in the prescribing information to determine the required number of packets, volume of water needed to reconstitute the powder from the packet(s), and individual volume that is administered 3 times a day. • Refer to the prescribing information for preparation instructions, as well as dosage and administration modifications and monitoring. • The pharmacokinetics of treatment have not been assessed in patients with mild renal impairment, but plasma concentrations of treatment increased

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				in patients with moderate or severe renal impairment. An appropriate dosage adjustment in patients with renal impairment could not be determined.

See the current prescribing information for full details.

Clinical Efficacy Summary

- 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* is a prospective, open-label, single-arm study that included patients (N=47) with genetically confirmed TK2d previously treated with pyrimidine nucleosides.
  - 38 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 260-800mg/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 800mg/kg/day.
- *Study 1* was a retrospective chart review study in patients (N=38) with genetically confirmed TK2d treated with pyrimidine nucleosides.
  - 29 of these patients had an age of TK2d symptom onset ≤12 years; none of the 29 patients discontinued treatment.
  - 35 of these 38 patients were later enrolled in Trial 1 to receive 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 160-800mg/kg/day.
- *Study 2* was a retrospective chart review study in patients (N=61) with genetically confirmed TK2d (43 untreated patients and 18 patients treated with pyrimidine nucleoside therapy).
  - 9 of these 61 patients were also included in the expanded access program and 1 patient was included in Study 1.
  - 27 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.
  - 22 untreated patients were included in the untreated external control group used to assess 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 200-1200mg/kg/day.
- The expanded access program data included patients (N=43) receiving Kygevvi; 9 patients were included in Study 2.
- Efficacy results are as follows.
  - 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.
- Of the 78 treated patients included in the survival analysis, 54% were male, 82% were White, 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 762mg/kg/day (range 260 to 800mg/kg/day).
- Results suggested that treatment reduced the overall risk of death from treatment start by approximately 86%.
  - Results are presented in the table below, which was adapted from the prescribing information.

Table 3. Efficacy results

Endpoint	Treated Patients (N=78)	Matched Untreated Patients (N=78)
Number of deaths (%)	3 (3.8%)	28 (35.9%)
Restricted mean survival time in years:		
At 4 years post treatment start	3.8	2.6
At 6 years post treatment start	5.8	3.7
At 10 years post treatment start	9.6	5.7
Hazard Ratio (HR) for risk of death from treatment start	0.14	

- Note: Treated patients were matched 1:`1 to untreated patients by category of age of TK2d symptom onset (≤2 years or >2 to ≤12 years). Within each category of age of symptom onset, the matching was performed as follows: treated patients were sorted in descending order, per their age of treatment initiation; the first treated patient in the sorted list was matched with the sorted untreated patient having the highest last known age; this matched untreated patient was then no longer available for matching with any remaining treated patients; the procedure continues in order through the sorted list of treated patients. Time of treatment start in the untreated patient was set to that of the matched treated patient.

Clinical guidelines

- While it is noted that specific guidelines for TK2d are not currently available, it is suggested to assess growth, weight, lung function, and neurodevelopment at physician visits (*Rare Disease Advisor Guidelines 2025*).

Safety summary

- **Contraindications:** None.

- **Box Warning:** None.

- **Warnings and precautions:**
  - Elevated liver transaminase (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) levels were reported in patients treated with Kygevvi.
    - Obtain baseline liver transaminase (ALT, AST) and total bilirubin levels in patients prior to treatment initiation with Kygevvi. If signs or symptoms consistent with liver injury are observed, interrupt treatment with Kygevvi until liver

transaminase (ALT, AST) and total bilirubin levels have either returned to baseline or stabilized at a new baseline value.
    - Consider permanently discontinuing Kygevvi if signs or symptoms consistent with liver injury persist or worsen.
    - Monitor liver transaminases and total bilirubin levels yearly and as clinically indicated.
  - Diarrhea and vomiting leading to hospitalization, dose reduction, and permanent discontinuation were reported in patients treated with Kygevvi.
    - Based on the severity of the diarrhea and/or vomiting, reduce the dosage of Kygevvi or interrupt treatment until diarrhea and/or vomiting improves or returns to baseline. Consider restarting Kygevvi at the last tolerated dose, and increase the dose as tolerated.
    - For persistent or recurring diarrhea and/or vomiting, consider discontinuing Kygevvi permanently and provide supportive care with electrolyte repletion as clinically indicated.

- **Common adverse drug reactions**:
  - Listed % incidence for adverse drug reactions= reported % incidence for drug (Kygevvi or pyrimidine nucleosides) Please note that there was no placebo data to compare with in the prescribing information.
    - The most frequently reported adverse events included diarrhea (72%), abdominal pain (including abdominal pain upper; 23%), vomiting (21%), alanine aminotransferase (ALT) increased (21%), and aspartate aminotransferase (AST) increased (17%).

- **Drug interactions:** None.

- **Special populations:**
  - There is no pregnancy category for this medication; however, the risk summary indicates that there are no available data on use during pregnancy to assess for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Endogenous pyrimidine nucleosides are transported across the placenta.
    - There are risks for adverse maternal and fetal outcomes during pregnancy with mitochondrial myopathies, including TK2 deficiency.
  - The safety and efficacy of use have been established in the pediatric population with an age of symptom onset on or before 12 years.

Conclusion

- Thymidine kinase 2 deficiency (TK2d) is caused by pathogenic variants in the nuclear thymidine kinase 2 (TK2) gene. The effect is depletion and numerous deletions of mitochondrial DNA (*O'Ferrall 2025*).
  - Clinically, TK2d displays as a progressive mitochondrial myopathy that generally starts in childhood.
- Kygevvi is a combination of doxecitine and doxribtimine, both pyrimidine nucleosides, 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.
  - Obtain baseline liver transaminase and total bilirubin levels in patients prior to treatment initiation. If signs or symptoms consistent with liver injury are observed, interrupt treatment. Monitor liver transaminases and total bilirubin levels yearly and as clinically indicated.
- Reduce Kygevvi dosage or interrupt treatment based on severity of diarrhea and/or vomiting.
- The efficacy of Kygevvi was established based on data from one phase 2 clinical study, 2 retrospective chart review studies, and an expanded access program, with overall survival being assessed.
  - Treatment reduced the overall risk of death from treatment start by about 86%.
- Kygevvi is the only FDA approved treatment for early-onset TK2d.

- It is recommended that Kygevvi should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

- **PDL Placement:**
  - ☐ Preferred
  - ☒ Non-Preferred

References

- Atwal PS, Barron SA. Overview of metabolic myopathies. Dynamed website. Last updated April 22, 2026. Accessed June 16, 2026. www.dynamed.com.
- Kygevvi. Package insert. UCB, Inc; November 2025.
- O'Ferrall EK. Mitochondrial myopathies: Clinical features and diagnosis. UpToDate website. Last updated April 27, 2026. Accessed June 16 2026. https://www.uptodate.com.
- Rare Disease Advisor Guidelines. Thymidine Kinase 2 Deficiency (TK2d). Last updated March 18, 2025. Accessed June 16, 2026. https://www.rarediseaseadvisor.com/disease-info-pages/thymidine-kinase-2-deficiency-guidelines/.

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