HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KYGEVVI safely and effectively. See full prescribing information for KYGEVVI.

KYGEVVI (doxecitine and doxribtimine) powder, for oral solution
Initial U.S. Approval: 2025

----------INDICATIONS AND USAGE----------
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. (1)

----------DOSAGE AND ADMINISTRATION----------
- Obtain baseline transaminase (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) levels in all patients prior to treatment initiation. (2.1)
- Recommended dosage (2.2):

KYGEVVI Dosage Level	KYGEVVI Dosage (mg/kg/day)
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. (2.2)
- Administer KYGEVVI orally in 3 equally divided doses with food. (2.2)
- See full prescribing information for dosage and administration modifications, monitoring, and preparation and administration instructions. (2.4)
- Use KYGEVVI only with ZX2000 administration kit. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------
Powder for oral solution: 2 g doxecitine and 2 g doxribtimine. (3)

----------CONTRAINDICATIONS----------
- None. (4)

----------WARNINGS AND PRECAUTIONS----------
- *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. (5.1)
- *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. (5.2)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥5%) are diarrhea, abdominal pain (including abdominal pain upper), vomiting, alanine aminotransferase increased (ALT), and aspartate aminotransferase increased (AST). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact UCB, Inc. at 1-844-599-2273 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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.

2 DOSAGE AND ADMINISTRATION

2.1 Important Recommendation Prior to KYGEVVI Treatment Initiation

Obtain baseline liver transaminase (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) and total bilirubin levels in patients prior to treatment initiation with KYGEVVI *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)]*.

2.2 Recommended Dosage

The recommended dosage of KYGEVVI is based on the patient's weight (Table 1). Titrate to the next dosage level based on tolerability after a minimum of 2 weeks at the current dosage level.

Table 1: Recommended Starting, Intermediate, and Maintenance Dosage of KYGEVVI

KYGEVVI Dosage Level	KYGEVVI Dosage (mg/kg/day)
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)

Administer KYGEVVI orally in 3 equally divided doses approximately 6 hours apart (plus or minus 2 hours) with food *[see Clinical Pharmacology (12.3)]*.

After calculating the daily dose, use Table 2 to determine the required number of KYGEVVI packets, volume of water needed to reconstitute the powder from the packet(s), and individual volume that is administered 3 times a day *[see Dosage and Administration (2.4)].*

2.3 Dosage and Administration Modifications and Monitoring

Liver Test Abnormalities

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 re-starting KYGEVVI at the last tolerated dose and increase the dose based on tolerability *[see Dosage and Administration (2.2)]*. 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 *[see Warnings and Precautions (5.1)]*.

Gastrointestinal

Based on the severity of the diarrhea and/or vomiting, reduce the dose of KYGEVVI or interrupt treatment until diarrhea and/or vomiting improves or returns to baseline. Consider re-starting KYGEVVI at the last tolerated dose and increase the dose based on tolerability *[see Dosage and Administration (2.2)]*. For persistent or recurring diarrhea and/or vomiting, consider discontinuing KYGEVVI permanently. Monitor for dehydration and treat promptly with electrolyte replacement *[see Warnings and Precautions (5.2)]*.

2.4 Preparation and Administration Instructions

Use Table 2 for preparation and administration information.

Table 2: Recommended Dosage - Preparation and Dosing by Daily-Dose Range

Total Daily Dose (mg/day)	Volume of Solution (mL) (administered 3 times per day)	Total mL of Water for Reconstitution	Total Number of KYGEVVI Packets for Reconstitution
750 – 824	2.5	40	1
825 – 974	3		
975 – 1,124	3.5		
1,125 – 1,299	4		
1,300 – 1,449	4.5		
1,450 – 1,649	5		
1,650 – 1,949	6		
1,950 – 2,249	7		
2,250 – 2,549	8		
2,550 – 2,849	9		
2,850 – 3,149	10		
3,150 – 3,449	11		
3,450 – 3,749	12		
3,750 – 4,049	13		
4,050 – 4,349	14	80	2
4,350 – 4,649	15		
4,650 – 4,949	16		
4,950 – 5,249	17		
5,250 – 5,549	18		
5,550 – 5,849	19		
5,850 – 6,149	20		
6,150 – 6,449	21		
6,450 – 6,749	22		
6,750 – 7,049	23		
7,050 – 7,349	24		
7,350 – 7,649	25		
7,650 – 7,949	26		
7,950 – 8,249	27*		
8,250 – 8,549	28	120	3
8,550 – 8,849	29		
8,850 – 9,749	30		
9,750 – 11,249	35		
11,250 – 12,749	40		

Total Daily Dose (mg/day)	Volume of Solution (mL) (administered 3 times per day)	Total mL of Water for Reconstitution	Total Number of KYGEVVI Packets for Reconstitution
12,750 – 14,249	45	160	4
14,250 – 15,749	50		
15,750 – 17,249	55*		
17,250 – 18,749	60	200	5
18,750 – 20,249	65		
20,250 – 21,749	70*		
21,750 – 23,249	75	240	6
23,250 – 24,749	80		
24,750 – 26,249	85	280	7
26,250 – 27,749	90		
27,750 – 29,249	95*		
29,250 – 30,749	100	320	8
30,750 – 32,249	105		
32,250 – 33,749	110*		
33,750 – 35,249	115	360	9
35,250 – 36,749	120		
36,750 – 38,249	125*		
38,250 – 39,749	130	400	10
39,750 – 41,249	135*		
41,250 – 42,749	140*		
42,750 – 44,249	145	440	11
44,250 – 45,749	150*		
45,750 – 47,249	155*		
47,250 – 48,749	160	480	12
48,750 – 50,249	165*		
50,250 – 51,749	170*		
51,750 – 53,249	175*	520	13
53,250 – 54,749	180*		
54,750 – 56,249	185	560	14
56,250 – 57,749	190*		
57,750 – 59,249	195*		
59,250 – 60,749	200	600	15
60,750 – 62,249	205*		
62,250 – 63,749	210*		
63,750 – 65,249	215*	640	16
65,250 – 66,749	220*		
66,750 – 68,249	225*		

***** The volume of each individual dose, when multiplied by 3, may not match the corresponding water volume used in the preparation of the oral solution as the final volume of the reconstituted oral solution will increase after the powder from the packets is added to the water volume.

Use the ZX2000 administration kit provided separately to prepare and administer the prescribed dose *[see How Supplied/Storage and Handling (16)]*. Refer to the Instructions for Use for full preparation and administration information on use of KYGEVVI with the ZX2000 administration kit. Household devices such as measuring cups or spoons are not adequate measuring devices. KYGEVVI should be prepared and administered by adults only.

Preparation Instructions

Preparation of KYGEVVI with a liquid other than water has not been studied clinically and is not recommended.

1. Obtain the required number of KYGEVVI packets to prepare a one-day supply of solution each morning.
2. Use 40 mL of water per packet. Pour the prescribed volume of room temperature water (between 20ºC - 25ºC or 68ºF - 77ºF) into the mixing bottle.
3. Add the powder from the required number of KYGEVVI packets into the mixing bottle.
4. Screw the dosing cup tightly onto the mixing bottle and gently invert the mixing bottle back and forth at least 20 times. If powder remains, repeat until the powder dissolves.
5. The mixed solution may appear cloudy and have some residual powder (inactive ingredients) remaining at the bottom or top.

Administration Instructions

Oral Administration

1. Before each administration, gently invert the tightly closed mixing bottle slowly back and forth at least 3 times.
2. Use 1 of 2 methods (dosing cup or oral syringe) to administer KYGEVVI solution. Choose the method based on the volume of solution to be administered per dose.
3. Take KYGEVVI solution in 3 equally divided doses approximately 6 hours apart (plus or minus 2 hours) with food.
4. Do not administer another dose if the dose is spit out or if a complete dose is not taken. Take the next dose at the next scheduled time.
5. Discard any remaining KYGEVVI solution 16 hours after reconstitution or after taking or giving the 3 doses, whichever comes first.

Feeding Tube Administration

KYGEVVI is compatible with most commonly available feeding tubes. KYGEVVI is compatible with feeding tubes made with polyvinylchloride (PVC) free from DEHP (Phthalates), polyurethane (PUR), and silicone (SIL) material.

1. Follow the instructions of the feeding tube manufacturer to administer KYGEVVI.
2. Draw up the KYGEVVI solution using a syringe compatible with the feeding tube.
3. Administer the solution immediately through the feeding tube.
4. Flush any residual solution in the syringe or feeding tube until no solution is left. To flush the tube, a single flushing step with a volume of water equivalent to the tube’s priming volume is sufficient.
5. Discard any remaining KYGEVVI solution 16 hours after reconstitution or after taking or giving the 3 doses, whichever comes first.

2.5 Storage Instructions for Prepared KYGEVVI Solution

- Store reconstituted KYGEVVI solution at controlled room temperature between 20°C to 25°C (68°F to 77°F) or in the refrigerator between 2°C to 8°C (36°F to 46°F).
- Discard KYGEVVI solution 16 hours after reconstitution or after taking or giving the 3 doses, whichever comes first.

2.6 Missed Dose

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.

3 DOSAGE FORMS AND STRENGTHS

Powder for oral solution: 2 g doxecitine and 2 g doxribtimine as white to off-white powder in a single use packet.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Elevated Liver Transaminase Levels

Elevated liver transaminase [alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST)] levels were reported in patients treated with KYGEVVI *[see Adverse Reactions (6.1)]*. In Study 1, two patients permanently discontinued treatment with KYGEVVI upon recurrence of elevated liver enzymes after a rechallenge at a reduced dose.

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 *[see Dosage and Administration (2.3)]*.

5.2 Gastrointestinal Adverse Reactions

Diarrhea and vomiting leading to hospitalization, dose reduction, and permanent discontinuation were reported in patients treated with KYGEVVI *[see Adverse Reactions (6.1)]*.

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.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Elevated Liver Transaminase Levels *[see Warnings and Precautions (5.1)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of KYGEVVI was evaluated in a prospective, open-label, single-arm study in pediatric and adult patients with genetically confirmed TK2d previously treated with pyrimidine nucleosides (Trial 1). Additional safety information was derived from retrospective chart review studies (Study 1, Study 2) and from an expanded access program *[see Clinical Studies (14)]*.

Permanent discontinuation of KYGEVVI due to an adverse reaction occurred in 9% of patients (Trial 1, Study 1, and Study 2). The adverse reactions which resulted in permanent discontinuation of KYGEVVI in >2% of patients were diarrhea (3%) and elevated liver enzymes (3%). In the expanded access program, diarrhea resulted in permanent discontinuation in 2 patients.

Dose reductions of KYGEVVI due to an adverse reaction occurred in 22% of patients (Trial 1, Study 1, and Study 2). Adverse reactions which required dose reduction in >2% of patients included diarrhea (21%) and abdominal pain (3%).

Diarrhea resulted in hospitalization in 2 pediatric patients (Study 1 and expanded access program).

Adverse Reactions from Trial 1

A total of 47 patients, between the ages of 0.7 and 74 years of age at enrollment, received KYGEVVI or pyrimidine nucleosides dosages up to 800 mg/kg/day *[see Clinical Studies (14)]*. KYGEVVI is not approved for use in patients with an age of TK2d symptom onset > 12 years. The mean (SD) KYGEVVI or pyrimidine nucleosides exposure during Trial 1 was 6.6 (2) years.

Table 3 summarizes the adverse reactions reported in ≥ 5% patients treated with KYGEVVI or pyrimidine nucleosides.

Table 3: Adverse Reactions That Occurred in ≥5% Adult and Pediatric Patients with TK2d Treated with KYGEVVI or Pyrimidine Nucleosides (Trial 1)

Adverse reactions	Treated Patients (N=47) n (%)
Diarrhea	34 (72)
Abdominal pain (including abdominal pain upper)	11 (23)
Vomiting	10 (21)
Alanine aminotransferase increased (ALT)	10 (21)
Aspartate aminotransferase increased (AST)	8 (17)

Adverse reactions, vomiting and elevated liver transaminases, were observed in a higher percentage of pediatric patients than in adult patients. In Trial 1, vomiting occurred in 28% (9/32) of pediatric patients compared to 7% (1/15) of adult patients. Elevated liver transaminases occurred in 25% (8/32) for ALT and 22% (7/32) for AST of pediatric patients compared to 13% (2/15) for ALT and 7% (1/15) for AST of adult patients.

Laboratory Adverse Reaction

Elevated liver enzymes have been observed as a clinical manifestation of TK2d. In Trial 1 and Study 1, elevations in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) occurred in 28% (14/50) and 22% (11/50) of patients respectively. In Trial 1, of all the patients who started treatment with elevated AST/ALT at baseline, 5% had last post-baseline ALT values that were higher severity than the baseline severity while continuing treatment *[see Warnings and Precautions (5.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on KYGEVVI use during pregnancy to evaluate 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 (*see Clinical Considerations*). In animal reproduction studies, oral administration of doxecitine and doxribtimine to pregnant rats and rabbits during organogenesis resulted in maternal and fetal toxicities in the rabbit at dose exposures 1233 and 811 times the maximum recommended human dose (MRHD) of 400 mg/kg/day doxecitine and 400 mg/kg/day doxribtimine, respectively, based on plasma exposure, but were not observed in the rat (*see Data*).

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20% respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk
Mitochondrial myopathies are associated with increased adverse perinatal outcomes, including preterm birth, pre-eclampsia and gestational diabetes.

Data

Animal Data
In an embryofetal development study in pregnant rats, once daily oral doses of 200, 600, and 2000 mg/kg/day doxecitine and doxribtimine were administered throughout organogenesis between gestation day (GD) 7 to 17. No maternal or embryofetal toxicity was observed up to 2000 mg/kg/day (1223 times and 425 times the MRHD of doxecitine and doxribtimine, respectively, based on plasma exposure).

In an embryofetal development study in pregnant rabbits, once daily oral doses of 200, 600, and 2000 mg/kg/day doxecitine and doxribtimine were administered throughout organogenesis between GD 7 and GD 19. Marked maternal toxicity and fetal malformations (dilated aorta with an associated narrow pulmonary trunk) were observed at the highest dose (1233 times and 811 times the MRHD of doxecitine and doxribtimine, respectively, based on plasma exposure). The maternal and fetal no observed adverse effect level (NOAEL) in rabbits (600 mg/kg/day) was associated with maternal plasma exposures 729 times and 126 times the MRHD of 400 mg/kg/day doxecitine and 400 mg/kg/day doxribtimine, respectively.

8.2 Lactation

Risk Summary

There are no data on the presence of doxecitine and doxribtimine or its metabolites in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. Data from published literature reports the presence of nucleosides and nucleotides in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KYGEVVI and any potential adverse effects on the breastfed infant from KYGEVVI or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of KYGEVVI for the treatment of thymidine kinase 2 deficiency (TK2d) have been established in pediatric patients with an age of symptom onset on or before 12 years. Use of KYGEVVI for this indication in this population is supported by evidence from two retrospective studies (Study 1, Study 2), one open-label study (Trial 1), and an expanded access program in which a total of 68 patients 0.7 years of age to less than 17 years of age were treated *[see Clinical Studies (14)]*.

In Trial 1, compared to adults, a higher percentage of pediatric patients experienced adverse reactions of vomiting and elevated liver transaminases *[see Adverse Reactions (6.1)]*. Serious adverse reactions in the pediatric population included hospitalization due to diarrhea in two patients *[see Warnings and Precautions (5.2)]*.

8.5 Geriatric Use

Clinical studies of KYGEVVI did not include sufficient number of patients 65 years of age and older to determine whether they respond differently from younger adult patients.

8.6 Renal Impairment

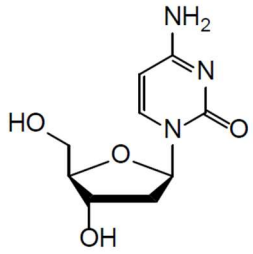
Plasma concentrations of doxecitine and doxribtimine increased in patients with moderate or severe renal impairment. The pharmacokinetics (PK) of doxecitine and doxribtimine have not been evaluated in patients with mild renal impairment. An appropriate dosage adjustment of KYGEVVI in patients with renal impairment could not be determined because renal impairment had distinct effects on the PK of doxecitine and PK of doxribtimine, and it is not feasible to separately adjust the dosage for doxecitine or doxribtimine contained in KYGEVVI *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

KYGEVVI is a combination of doxecitine and doxribtimine, both of which are pyrimidine nucleosides. KYGEVVI is a powder for oral solution. Both doxecitine and doxribtimine are white to off-white powders and soluble in water.

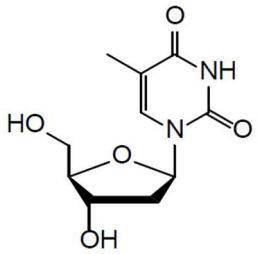
Doxecitine

The chemical name of doxecitine is 4-Amino-1-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidin-2(1H)-one. The molecular formula is $C_9H_{13}N_3O_4$ and the molecular weight is 227.22 g/mol. The chemical structure is:



Doxribtimine

The chemical name of doxribtimine is 1-((2R,4S,5R)-4-Hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione. The molecular formula is $C_{10}H_{14}N_2O_5$ and the molecular weight is 242.23 g/mol. The chemical structure is:



Each packet of KYGEVVI powder contains 2 grams doxecitine and 2 grams doxribtimine. The inactive ingredients are colloidal silicon dioxide and magnesium stearate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Administration of KYGEVVI 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.

12.2 Pharmacodynamics

The exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of KYGEVVI have not been fully characterized.

12.3 Pharmacokinetics

Following oral administration of doxecitine and doxribtimine in healthy adult subjects, the baseline-adjusted maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) increased in a less than dose proportional manner for doxecitine at doses ranging from 43 mg/kg to 133 mg/kg and more than dose proportional manner for doxribtimine at doses ranging from 43 mg/kg to 133 mg/kg. There is minimal or no accumulation of doxecitine and doxribtimine following multiple dose administrations. Following oral administration of doxecitine and doxribtimine at the recommended maintenance dosage of 800 mg/kg/day under fed conditions in 18 TK2d pediatric and adult subjects, the estimated baseline-unadjusted geometric mean C_{max} at steady state was 12 ng/mL and 19 ng/mL for doxecitine and doxribtimine, respectively, and the geometric mean AUC from time 0 to 24 hours ($AUC_{0\text{-}24hr}$) was 108 ng·h/mL and 191 ng·h/mL for doxecitine and

doxribtimine, respectively. Inter-subject variability (geometric CV%) in C_{max} and AUC_{0-24h} values of doxecitine and doxribtimine were greater than 70%.

Absorption

The absolute bioavailability of doxecitine and doxribtimine following oral administration has not been determined. The median time to peak plasma concentration (T_{max}) was approximately 2 hours for doxecitine and 4 hours for doxribtimine.

Effect of Food
Following an oral administration of 133 mg/kg doxecitine and 133 mg/kg doxribtimine with a high-fat, high-calorie meal in healthy adult subjects, baseline-adjusted plasma C_{max} and AUC_{0-t} increased by 79% and 137%, respectively, for doxecitine; and increased by 27% and 74%, respectively, for doxribtimine, compared to fasted conditions *[see Dosage and Administration* (2.2)*]*.

Distribution

In vitro plasma protein binding of doxecitine and doxribtimine was less than 10% over the concentration range between 0.23 mcg/mL and 23 mcg/mL.

Elimination

The mean half-life was approximately 1 hour for doxecitine and 5 hours for doxribtimine following a single oral administration of 133 mg/kg doxecitine and 133 mg/kg doxribtimine under fed conditions in healthy adult subjects.

Metabolism
Doxecitine and doxribtimine are primarily degraded (catabolized) by cytidine deaminase and thymidine phosphorylase, respectively, to their nucleobases and the 2-deoxy-α-D-ribose 1-phosphate moiety. Intermediate products of doxecitine catabolism are deoxyuridine, uracil, and dihydrouracil with the end products β-alanine, ammonia, and carbon dioxide (CO_2). Thymine, the pyrimidine nucleobase of doxribtimine, is subsequently catabolized to dihydrothymine and ultimately to γ-amino-isobutyric acid and CO_2.

Doxecitine and doxribtimine are not known to be metabolized by cytochrome P450 (CYP) isoforms.

Excretion
Urinary excretion of intact doxecitine and doxribtimine was <1% of the dose in healthy subjects following an oral administration of doxecitine and doxribtimine.

Specific Populations

Male and Female Patients
The pharmacokinetics of doxecitine and doxribtimine were not significantly different between male and female subjects.

Patients with Renal Impairment
The pharmacokinetics of doxecitine and doxribtimine in subjects with moderate (estimated glomerular filtration rate [eGFR] ≥ 30 and ≤ 59 mL/min/1.73 m^2) or severe (eGFR ≥ 15 and ≤ 29 mL/min/1.73 m^2) renal impairment were compared with healthy subjects with normal renal function following a single oral administration of 133 mg/kg doxecitine and 133 mg/kg doxribtimine. Baseline-adjusted plasma doxecitine AUC was 122% and 66% higher in subjects with moderate and severe renal impairment, respectively, compared with matched control subjects with normal renal function. Baseline adjusted plasma doxribtimine AUC was 447% and 148% higher in subjects with moderate and severe renal impairment, respectively, compared with matched control subjects with normal renal function *[see Use in Specific Populations (8.6)]*.

Patients with Hepatic Impairment
No studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of doxecitine and doxribtimine.

Drug Interaction Studies

In Vitro Studies
CYP enzymes: Doxecitine and doxribtimine are not inducers, inhibitors, or substrates of CYP isozymes at clinically relevant concentrations.

Transporter systems: Doxecitine and doxribtimine do not inhibit P-glycoprotein (P-gp), BCRP, BSEP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2-K at clinically relevant concentrations. Doxribtimine may be a substrate of BCRP, but its clinical significance is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Animal studies to evaluate the carcinogenic potential of doxecitine and doxribtimine have not been conducted.

Mutagenesis

Doxecitine and doxribtimine were not mutagenic or clastogenic in an *in vitro* bacterial reverse mutation (Ames) and an *in vivo* rat micronucleus assay. Doxecitine and doxribtimine induced chromosomal aberrations in the absence of metabolic activation in an *in vitro* cytogenetic study in human lymphocytes. One compound (alpha-hydroxythymidine) originating from a doxribtimine starting material and present in the final drug product was positive for mutagenesis in the Ames assay and positive for clastogenesis in human peripheral lymphocytes when tested alone.

Impairment of Fertility

Doxecitine and doxribtimine had no effect on male or female fertility or early embryonic development at doses up to 2000 mg/kg/day in rats (1131 times and 1223 times the MRHD in males and females respectively for 400 mg/kg/day doxecitine and 1056 times and 425 times the MRHD in males and females respectively for 400 mg/kg/day doxribtimine, based on plasma exposure).

14 CLINICAL STUDIES

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 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.

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.

Of the 78 treated patients included in the survival analysis, 54% were male and 36% were of Hispanic or Latino ethnicity. Eighty-two percent of patients were White, 4% Black or African American, 5% Asian, 3% Other, and 1% American Indian or Alaska Native. 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% (95% CI: 61%, 96%) (Table 4, Figure 1).

Table 4: Overall Survival in Patients with TK2d (Age of Symptom Onset ≤12 Years) Treated with KYGEVVI Versus Matched Untreated Patients (External Control)[a]

	Treated Patients (n= 78)	Matched Untreated Patients (n=78)
Number of Deaths (%) [b]	3 (3.8%)	28 (35.9%)
Restricted Mean Survival Time in Years (95% CI) [b, c]		
• **At 4 years post treatment start**	• 3.8 (3.7, 4)	• 2.6 (2.2, 3)
• **At 6 years post treatment start**	• 5.8 (5.5, 6)	• 3.7 (3, 4.3)
• **At 10 years post treatment start**	• 9.6 (9.2, 10)	• 5.7 (4.5, 6.9)
Hazard Ratio [d] **For Risk of death from treatment start (95%CI)**	0.14 (0.04, 0.39)	

CI: Confidence Interval

(a) Treated patients were originally from Trial 1 (n=9), Study 1 (n=27), Study 2 (n=11), and the expanded access program (n=31). Untreated patients were from published literature (n=57) and Study 2 (n=21).

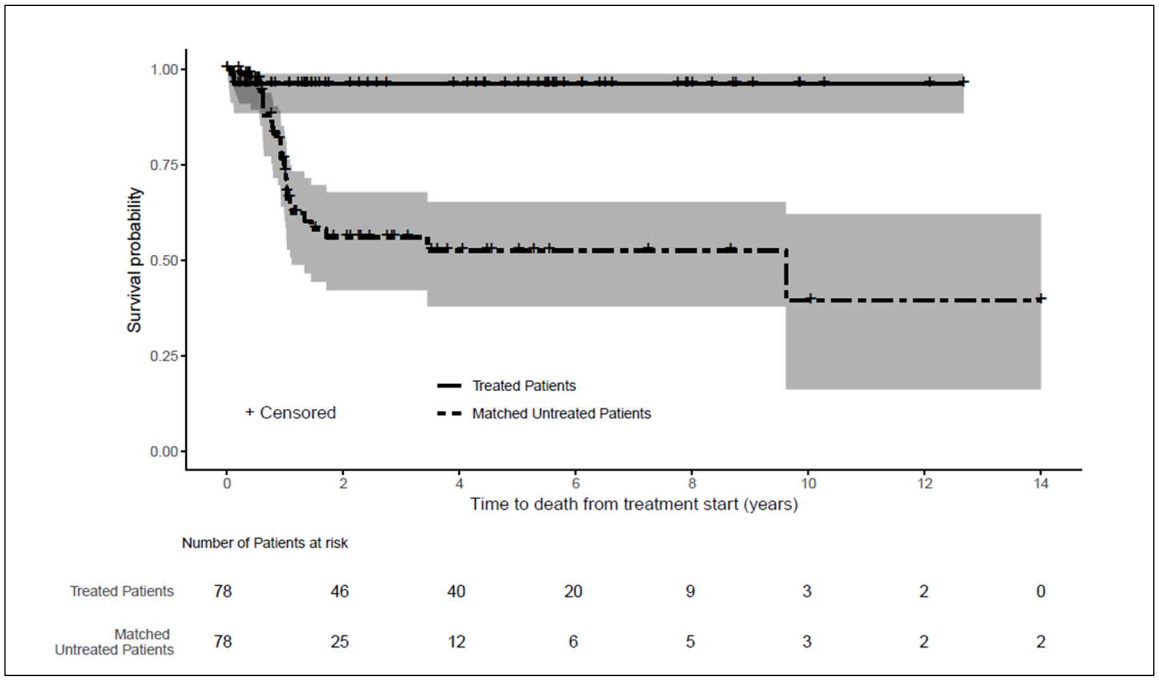
(b) An additional censoring step for untreated subjects was performed for each matched pair where the untreated subject died and had a longer follow-up time than the matched treated subject who was censored. The follow-up time of the untreated subject was then censored at the follow-up time of the treated subject.

(c) Based on the area under the survival curves up to 4-, 6-, 10-years post treatment start.

(d) Estimates based on Cox Proportional Hazard Model with Firth correction that includes matched pair as a strata, age of symptom onset as a continuous covariate, and treatment (treated or untreated) as a time independent variable.

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, according to 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.

Figure 1: Kaplan-Meier Survival Curves for Time to Death from Treatment Start in Patients with TK2d Treated with KYGEVVI and Matched Untreated Patients (External control) [(a,b)]



(a)Treated patients were from Trial 1, Study 1, Study 2, and the expanded access program. Untreated patients were from published literature and Study 2.
(b) Kaplan-Meier Curves with 95% confidence intervals using log-log transformation and with treatment group as strata variable; Age of TK2d Symptom Onset ≤ 12 years. An additional censoring step for untreated subjects in the footnote (b) of Table 4 was performed.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

KYGEVVI is supplied as follows:

Package 1 of 2
NDC 50474-350-01: Each single use packet contains 4 g of KYGEVVI as a white to off-white powder (2 g doxecitine and 2 g doxribtimine)
NDC 50474-350-30: Carton contains 30 packets

Package 2 of 2
The ZX2000 administration kit for use with KYGEVVI is supplied separately and contains the following:

- One dosing system (includes mixing bottle and dosing cup)
- Two 10 mL oral syringes
- Two spare seals

Storage and Handling

Store KYGEVVI packets at 20°C to 25°C (68°F to 77°F); excursion permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Store reconstituted KYGEVVI solution at controlled room temperature or in the refrigerator. Discard KYGEVVI solution 16 hours after reconstitution or after taking or giving the 3 doses, whichever comes first *[see Dosage and Administration (2.5)].*

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Preparation and Administration Instructions of KYGEVVI Solution

Advise the patient to use the ZX2000 administration kit provided by the pharmacy to prepare and administer KYGEVVI solution.

Inform the patient to prepare a one-day supply of the KYGEVVI solution each morning and take each individual dose with food *[see Dosage and Administration (2.4)].*

Elevated Liver Transaminase Levels

Inform the patient that KYGEVVI may cause liver enzyme elevations. Instruct the patient to promptly report loss of appetite, abdominal pain, dark urine, or jaundice to his/her healthcare provider *[see Warnings and Precautions (5.1)].*

Gastrointestinal Adverse Reactions

Inform the patient that KYGEVVI may cause diarrhea and vomiting. Advise the patient to promptly report to his/her healthcare provider diarrhea and vomiting that lasts longer than a few days while taking KYGEVVI *[see Warnings and Precautions (5.2)].*

KYGEVVI manufactured for:
UCB, Inc.
Smyrna, GA 30080