Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed medicines and medicines used outside their licence, to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life-threatening conditions where there are no adequate treatment options. More information about the scheme can be found here: http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the EAMS medicine. This medicine does not yet have a licence (marketing authorisation) and the information is provided to assist the clinician in prescribing this unlicensed medicine. Guidance on prescribing unlicensed medicines can be found on the GMC webpage:
https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

The scientific opinion is based on assessment of the information supplied to the MHRA on the benefits and risks of this promising new medicine. As such, this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to license such a medicine.

The prescribing clinician should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

Scientific opinion period: The MHRA will withdraw the EAMS positive scientific opinion when a marketing authorisation (drug licence) is issued for the EAMS product covering the EAMS indication, or if following scientific assessment, the EAMS criteria are considered to be no longer met.

Treatment protocol update(s): In case of substantial new efficacy or safety data, the treatment protocol may need to be updated.

Contact information regarding queries on using this EAMS medicine can be found at the end of this document.

Information for the healthcare professionals

1. NAME OF THE MEDICINAL PRODUCT

Doxecitine and doxribtimine 4 g powder for oral solution (2 g each)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The drug product, doxecitine and doxribtimine powder for oral solution, contains 2 drug substances (2 g doxecitine and 2 g doxribtimine) formulated with excipients (silicon dioxide and magnesium stearate) as a white to off-white powder suitable for reconstitution in water, for oral administration as nucleoside therapy.

Both excipients used in the drug product formulation are chemically inert. Colloidal silica anhydrous (silicon dioxide) is added as a glidant, and magnesium stearate is added as a lubricant to aid in the mechanical filling of unit dose packages.

3. PHARMACEUTICAL FORM

Doxecitine and doxribtimine powder for oral solution for administration orally or via a feeding tube.

Two drug substances formulated with excipients as a solid white-to-off-white powder suitable for reconstitution in water.

The reconstituted solution is opalescent and colourless.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of paediatric and adult patients with thymidine kinase 2 deficiency (TK2d) with an age of symptom onset on or before 12 years.

4.2 Posology and method of administration

Posology
Dosing for doxecitine and doxribtimine is based on weight of the patient; reassessment of weight should be performed by the prescribing physician.
Doxecitine and doxribtimine is titrated and dosed based on individual patient tolerability, up to a maximum recommended maintenance dose of 800mg/kg/day (400 mg/kg/day of doxecitine and 400 mg/kg/day of doxribtimine).

Doxecitine and doxribtimine should be administered every day in 3 equal doses with food.

The initial dose of doxecitine and doxribtimine is 260mg/kg/day (130mg/kg/day of doxecitine and 130mg/kg/day of doxribtimine), TID (3 equal doses with food). If the tolerability is acceptable after 2 weeks (Day 15), the dose can be increased to 520mg/kg/day (260mg/kg/day of doxecitine and 260mg/kg/day of doxribtimine).

If the tolerability remains acceptable after an additional 2 weeks of dosing (Day 29), the dose can be increased again to the maintenance dose of 800mg/kg/day (400mg/kg/day of doxecitine and 400mg/kg/day of doxribtimine). The total administered dose will be selected according to the patient's weight.

Table 1: Recommended dosing schedule[1]:

Initial dosage	130 mg/kg/day of doxecitine and 130 mg/kg/day of doxribtimine
Day 14 Intermediate Dosage	260 mg/kg/day of doxecitine and 260 mg/kg/day of doxribtimine
Day 28 Maintenance Dosage	400 mg/kg/day of doxecitine and 400 mg/kg/day of doxribtimine

[1]For patients with moderate or severe renal impairment a slower titration (at least 4 weeks between each dose increase) should be used.

Tables 2, 3, 4 and 5 show the appropriate number of doxecitine and doxribimtine powder sachets and required dilution volume by body weight for the recommended dosage levels.

For information relating to the re-challenge of doxecitine and doxribtimine after meeting liver-related drug discontinuation criteria, see Additional information.

Special populations

There is limited data on the pharmacokinetics (PK), safety, and efficacy of doxecitine and doxribtimine in study participants 65 years of age and older.

There is no experience with the use of doxecitine and doxribtimine in patients with TK2d who have impaired renal function. Systemic exposures to the active pharmaceutical ingredients deoxycytidine (dC) and deoxythymidine (dT) following a single dose of doxecitine and doxribtimine are significantly increased in adult volunteers with moderate (eGFR ≥30 and ≤59mL/min/1.73m^2 by Modification of Diet in Renal Disease [MDRD]) or severe renal impairment (eGFR ≥15 and ≤29mL/min/1.73m2 by MDRD) when compared with matched healthy control study participants with normal renal function (MT-1621-106). Patients with TK2d who have impaired renal function were not specifically excluded from clinical studies of the constituent nucleos(t)ides in doxecitine and doxribtimine. Patients with renal impairment who are administered doxecitine and doxribtimine should be monitored carefully. Potential risks associated with long-term treatment with doxecitine and doxribtimine in patients with impaired renal function remain unknown.

The effect of hepatic impairment on the PK of doxecitine and doxribtimine is not known. There is no experience with the use of doxecitine and doxribtimine in patients with TK2d who have impaired hepatic function. Patients with elevated transaminases and/or past or current hepatic impairment should be evaluated carefully before initiation of treatment.

Method of Administration

The daily dose of doxecitine and doxribtimine should be reconstituted in water and administered as 3 equal divided doses orally or reconstituted with water for administration via enteral feeding tube approximately 6 (±2) hours apart. Doxecitine and doxribtimine should be administered with food.

Table 2: Recommended initial dosage 130 mg/kg/day of doxecitine and 130 mg/kg/day of doxribtimine oral solution preparation and dosing based on body weight

Body weight (kg)	Daily oral solution preparation		Individual dose volume (ml) (administered 3 times per day)
	Number of sachet(s) for reconstitution[b]	Water volume (ml)[a]	
3.0 – 3.4	1	40	2.5
3.5 - 3.9			3
4.0 - 4.4			3.5
4.5 - 4.9			4
5.0 - 5.9			4.5
6.0 - 6.9			5.5
7.0 - 7.9			6
8.0 - 8.9			7
9.0 - 10.4			8
10.5 - 11.9			10
12.0 - 13.9			11
14.0 - 15.9			13
16.0 - 17.4	2	80	14
17.5 - 18.9			16
19.0 - 20.9			17
21.0 - 24.9			20
25.0 - 27.9			22
28.0 - 31.9			25
32.0 - 34.9	3	120	28
35.0 - 37.9			30
38.0 - 41.9			35
42.0 - 47.9			40
48.0 - 54.9	4	160	45
55.0 - 61.9			50
62.0 - 72.9			55[c]
73.0 - 84.9	5	200	65
85.0 – 92.9	6	240	75
93.0 – 109.9	7	280	85
110.0 – 120.0	8	320	100

[a]Volume of water to reconstitute the powder for the preparation of one day's supply of reconstituted oral solution.
[b]The number indicates the number of sachets needed for one day supply preparation of reconstituted oral solution.
[c]The volume of each individual dose, when multiplied by three, may not match the indicated total daily water volume, this is not an error. Final volume of the reconstituted oral solution will increase after the powder of the prescribed number of sachets is added to the water volume.

Table 3: Recommended day 14 intermediate dosage 260 mg/kg/day of doxecitine and 260 mg/kg/day of doxribtimine oral solution preparation and dosing based on body weight

Body weight (kg)	Daily oral solution preparation		Individual dose volume (ml) (administered 3 times per day)
	Number of sachet(s) for reconstitution[b]	Water volume (ml)[a]	
3.0 - 3.4	1	40	5.5
3.5 - 3.9			6.5
4.0 - 4.4			7.5
4.5 - 4.9			8
5.0 - 5.9			9.5
6.0 - 6.9			11
7.0 - 7.9			13
8.0 - 8.9	2	80	14
9.0 - 10.4			17
10.5 - 11.9			19
12.0 - 13.9			22
14.0 - 15.9			26
16.0 - 17.4	3	120	29
17.5 - 18.9			30
19.0 - 20.9			35
21.0 - 24.9			40
25.0 - 27.9	4	160	45
28.0 - 31.9			50
32.0 - 34.9			55[c]
35.0 - 37.9	5	200	65
38.0 - 41.9			70[c]
42.0 - 47.9	6	240	75
48.0 - 54.9	7	280	90
55.0 - 61.9	8	320	100
62.0 - 72.9	9	360	115
73.0 - 84.9	10	400	135[c]
85.0 - 92.9	11	440	155[c]
93.0 – 109.9	13	520	175[c]
110.0 – 120.0	15	600	200

[a]Volume of water to reconstitute the powder for the preparation of one day's supply of reconstituted oral solution.
[b]The number indicates the number of sachets needed for one day supply preparation of reconstituted oral solution.
[c]The volume of each individual dose, when multiplied by three, may not match the indicated total daily water volume, this is not an error. Final volume of the reconstituted oral solution will increase after the powder of the prescribed number of sachets is added to the water volume.

Table 4: Recommended day 28 maintenance dosage 400 mg/kg/day of doxecitine and 400 mg/kg/day of doxribtimine oral solution preparation and dosing based on body weight

Body weight (kg)	Daily oral solution preparation		Individual dose volume (ml) (administered 3 times per day)
	Number of sachet(s) for reconstitution[b]	Water volume (ml)[a]	
3.0 - 3.4	1	40	9
3.5 - 3.9			10
4.0 - 4.9			12
5.0 - 5.9	2	80	15
6.0 - 6.9			17
7.0 - 7.9			20
8.0 - 8.9			22
9.0 - 10.4			26
10.5 - 11.9	3	120	30
12.0 - 13.9			35
14.0 - 15.9			40
16.0 - 17.4	4	160	45
17.5 - 18.9			50
19.0 - 20.9			55[c]
21.0 - 24.9	5	200	60
25.0 - 27.9			70[c]
28.0 - 31.9	6	240	80
32.0 - 34.9	7	280	90
35.0 - 37.9	8	320	100
38.0 - 41.9			110[c]
42.0 - 47.9	9	360	120
48.0 - 54.9	10	400	140[c]
55.0 - 61.9	12	480	160
62.0 - 72.9	13	520	180[c]
73.0 - 85.0	15	600	210[c]

[a]Volume of water to reconstitute the powder for the preparation of one day's supply of reconstituted oral solution.
[b]The number indicates the number of sachets needed for one day supply preparation of reconstituted oral solution.
[c]The volume of each individual dose, when multiplied by three, may not match the indicated total daily water volume, this is not an error. Final volume of the reconstituted oral solution will increase after the powder of the prescribed number of sachets is added to the water volume.

NOTE: There is very limited experience with patients weighing >85 kg. In case of a patient weighing >85.0 kg the total daily volume will exceed 640 ml and **the individual dose** of oral solution should be **prepared three times per day** instead of preparing the solution once per day**.**
When the individual dose volume exceeds 225 ml, it should be divided into two separate portions taken immediately one after the other. The Administration device kit dosing cup must be used to accurately measure and administer each portion.

Table 5: Recommended day 28 maintenance dosage of KYGEVVI oral solution preparation and dosing for patients weighing >85.0 kg

Body weight (kg)	Number of sachet(s) for reconstitution[b]	Water volume (ml)[a]	Individual dose volume (ml) (administered 3 times per day)
85.1 – 92.9	6	240	230
93.0 – 99.9			250[c]
100.0 – 109.9	7	280	270
110.0 – 120.0	8	320	300

[a]Volume of water to reconstitute the powder for the preparation of reconstituted oral solution.
[b]The number indicates the number of sachets needed for preparation of reconstituted oral solution.
[c]The volume of each individual dose may not match the indicated total water volume, this is not an error. Final volume of the reconstituted oral solution will increase after the powder of the prescribed number of sachets is added to the water volume.

- Prepare the oral solution using the recommended Administration device kit.
- Dissolve the prescribed number of powder sachets with room temperature water.
  - Use 40 ml of water per sachet.
  - Do not mix with any other medicinal products, liquids, powders or foods.
- Make a one-day supply of oral solution each morning or for a total daily volume exceeding 640 ml for patients weighing >85.0 kg, the solution should be prepared for each individual dose separately.
  - Pour the prescribed amount of water into the mixing bottle first. Then add the powder from the sachets.
  - Close the mixing bottle with the dosing cup, and turn it upside down and back at least 20 times to mix.
  - After administration, store the mixing bottle at room temperature or in the refrigerator.
- Before each administration, turn the mixing bottle slowly upside down and back at least 3 times.

Any remainder after the third dose of the day is taken should be discarded.

Training for administration of the product should be provided by either the treating physician or the Pharmacist if appropriate. Please refer to the Instructions for Use at the end of this document for further details on use of the product.

If a dose is missed, the dose should be taken as soon as possible. However, if it is within 2 hours to the next dose, the dose should not be taken. The patient should take the next dose at the usual time. A double or extra dose should not be taken to make up for the missed dose.

4.3 Contraindications

Hypersensitivity to any of the excipients listed in Section 6.1.

4.4 Special warnings and precautions for use

Though elevations in liver function tests may be related to TK2d, other possible causes of liver injury should be evaluated before treatment with doxecitine and doxribtimine. In particular, benefit-risk should be considered in patients with impaired bilirubin excretory or protein synthetic function due to the potential for increased risk of drug-induced liver injury.

Transaminases (alanine transaminase [ALT] and aspartate transaminase [AST]) should be closely monitored during initiation of treatment with doxecitine and doxribtimine and periodically thereafter. Consistent with general guidance for monitoring for drug-induced liver injury, doxecitine and doxribtimine should be discontinued if any of the following criteria are met (U.S. Food and Drug Administration Drug-Induced Liver Injury Guidance):

- ALT or AST >8×upper limit of normal (ULN)
- ALT or AST >5×ULN for more than 2 weeks
- ALT or AST >3×ULN **and** (serum total bilirubin >2×ULN or plasma prothrombin time or its international normalised ratio >1.5)
- ALT or AST >3×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Patients who meet these stopping criteria should be appropriately evaluated, and if alternative causality versus treatment with doxecitine and doxribtimine is identified, re-challenge with doxecitine and doxribtimine should be considered.

Diarrhoea has been reported as a frequent treatment-emergent adverse event and appears to be dose-related. The majority of events of diarrhoea were mild to moderate in severity, occurred mostly during treatment initiation, and generally were self-limiting or improved with dose reduction and longer duration of treatment at a lower dose before escalating back to the maintenance dose. Symptomatic treatment with antimotility agents could be considered, assessing individual patients' benefit versus risk (e.g., in paediatric population).

Other medicines and doxecitine and doxribtimine

Patients should inform the doctor or pharmacist if any other medicines are being taken or might be taken.

Doxecitine and doxribtimine with food, drink and alcohol

- This medicine must only be mixed with water by the patient
- Patients should not directly prepare the powder with food or other liquids.

4.5 Interaction with other medicinal products and other forms of interaction

No *in vivo* interaction studies have been performed in adult or paediatric patients. Certain cytotoxic and antiviral medicines (eg, cedazuridine, cisplatin, tipiracil, brivudine, stavudine, ribavarin, fludarabine) may interact with doxecitine and doxribtimine by affecting enzymes that metabolize doxecitine or doxribtimine, or nucleoside transporters. These interactions have not been observed in patients with TK2d treated with doxecitine and doxribtimine; their clinical significance is unknown.

While the overall potential for clinically relevant drug-drug interactions with doxecitine and doxribtimine is considered low based on nonclinical and clinical information, such interactions cannot be entirely excluded in some patients, particularly those with higher-than-typical systemic

exposure or receiving concomitant medicinal products that are sensitive CYP or transporter substrates.

Based on its mechanism of action, doxecitine and doxribtimine is not expected to reduce vaccine-specific immunoglobulin G. Immunisation with vaccines during doxecitine and doxribtimine treatment has not been studied and the response to immunisation with any vaccine is unknown.

If a coronavirus disease 2019 (COVID-19) vaccination is planned, a minimum of 72 hours between COVID-19 vaccination and doxecitine and doxribtimine administration should occur to allow for the differentiation of safety profiles. If any adverse events (AEs) occur, they should be handled as described in the patient treatment protocol with a causality assessment provided for both treatment and vaccination.

The use of non-GMP doxecitine and doxribtimine or deoxynucleoside monophosphates is prohibited while enrolled in the programme.

The use of any other investigational agents for treatment of TK2d is not permitted while the patient is participating in the programme.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data on the use of doxecitine and doxribtimine in pregnant women.
Endogenous pyrimidine nucleosides are transported across the placenta by placental nucleoside transporters to help meet the foetal requirements for nucleosides.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
The use of doxecitine and doxribtimine when planning for and during pregnancy may be considered if the clinical benefit outweighs the risk.

The patient should be withdrawn from the EAMS as soon as pregnancy is known (by positive serum pregnancy test).

The patient should complete the assessments outlined for the end of treatment Visit.
Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events (SAEs).

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy should be reported as an AE or SAE. A spontaneous abortion is always considered to be a SAE and should be reported as such. Any post-programme pregnancy-related SAE considered reasonably related to doxecitine and doxribtimine by the treating physician should be reported to the Sponsor. While the treating physician is not obligated to actively seek this information in former patients, he or she may learn of an SAE through spontaneous reporting.

Breast-feeding

It is unknown whether doxecitine and doxribtimine is excreted in human milk, but endogenous pyrimidine nucleosides and nucleotides are present naturally in human milk. At therapeutic doses of doxecitine and doxribtimine no effects on the breastfed newborns are anticipated. doxecitine and doxribtimine can be used during breast-feeding.

Fertility

The effect of doxecitine and doxribtimine on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility.

4.7 Effects on ability to drive and use machines

Doxecitine and doxribtimine is not likely to affect driving and/or the use of machinery.

4.8 Undesirable effects

Summary of the safety profile

The frequencies of adverse reactions are based on pooled data from clinical studies (MT-1621-101 and TK0102) in 50 patients, who were exposed to KYGEVVI during a median of 78.2 months (min 4, max 157), with a median maintenance dose of 387.2 mg/kg/day of doxecitine and 387.2 mg/kg/day of doxribtimine (min 170; max 400).

The most commonly reported adverse reactions were diarrhoea (86%), vomiting (28%), abdominal pain (including abdominal pain upper) (26%).

Tabulated list of adverse reactions

Adverse drug reactions (ADRs) from clinical studies are classified by the Medical Dictionary for Regulatory Activities System Organ Class and Preferred Term. Frequency is classified using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000). The low prevalence of TK2d and the small size of the medicinal product safety database do not allow for detecting ADRs that are classified as rare or very rare.

Table 6. Adverse drug reactions

System organ class	Frequency	Adverse reaction
Gastrointestinal disorders	Very common	Diarrhoea Vomiting Abdominal pain (including abdominal pain upper)

Gastrointestinal disturbances

Gastrointestinal disturbances such as diarrhoea, vomiting, and abdominal pain (including abdominal pain upper) are very commonly reported ADRs with doxecitine and doxribtimine treatment. The majority of events of diarrhoea were mild to moderate in severity and were generally self-limiting or improved with temporary dose reduction. None of the 50 participants who received treatment with doxecitine and doxribtimine in clinical studies MT-1621-101 and TK0102 discontinued due to gastrointestinal disturbances.

Diarrhoea, abdominal pain (including abdominal pain upper) and vomiting are not anticipated to affect the risk benefit balance of doxecitine and doxribtimine or have implications for public health.

Transaminases Increased

Post-treatment elevations in ALT and/or AST have been reported in Phase 2 clinical studies.

Most transaminase elevations were mild in intensity, generally ≤3x ULN, transient, not associated with concurrent total bilirubin elevation, and not treatment limiting. There was also no trend in the time to onset of post-treatment transaminases elevations. In 2 study participants

(2/50) with post-treatment ALT elevations >3xULN, their elevated liver enzymes ameliorated following temporary discontinuation of study drug but became elevated upon re-initiation of a reduced dose, resulting in their permanent discontinuation from the study.

As patients with TK2d may have pre-existing liver enzyme elevations to varying degree and potential treatment-related exacerbations of clinical relevance, though not observed in clinical studies, cannot be fully excluded to date, "transaminases increased" is considered an important potential risk.

4.9 Overdose

If a suspected ingestion of a higher dose of doxecitine and doxribtimine than prescribed occurs the patient should contact their physician for advice as soon as possible.

Oral doses of pyrimidine nucleos(t)ides >400mg/kg/day have not been intentionally administered to patients with TK2d. Higher doses might be associated with worsening of diarrhoea (see below). Based on experience with lower doses to date, these symptoms are anticipated to be self-limited and reversible with a decrease in dose and/or discontinuation of treatment. Symptomatic management may be required.

There have been 2 cases of accidental overdose reported. One patient received 1200mg/kg/day for 10 days which was above the maximum dose of 800mg/kg/day. One participant incorrectly ingested extra volumes of drug solution which correlated to an overdose of 2% of their 800mg/kg/day dose at 0 to 15 months, 4% at 15 to 24 months, and 2% at 24 to 25 months of the ongoing study. There were no adverse effects due to these dosing errors other than a worsening of existing diarrhoea (mild to moderate severity) in 1 participant, which is a known nonserious risk with the use of doxecitine and doxribtimine.

In the event of overdose, it is recommended that the patient is monitored closely for any signs and symptoms of adverse reactions and appropriate symptomatic treatment should be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

The primary mechanism of action of doxecitine and doxribtimine is the incorporation of nucleosides dC and dT into skeletal muscle mitochondrial deoxyribonucleic acid (DNA) to restore mitochondrial DNA copy number and improve skeletal muscle function in patients with TK2d. Doxecitine and doxribtimine utilise residual TK2 activity as well as the cytosolic phosphorylation pathway via thymidine kinase 1 [TK1] and deoxycytidine kinase [dCK] to increase mitochondrial DNA precursors (deoxycytidine Triphosphate (dCTP) and deoxythymidine Triphosphate (dTTP)) in the mitochondria.

Pharmacodynamic effects

No formal pharmacodynamic studies have been conducted with doxecitine and doxribtimine. Effects of doxecitine and doxribtimine on cardiac electrophysiology have not been determined in a formal clinical trial. Doxecitine and doxribtimine are chemically identical to ubiquitous endogenous nucleosides. Geometric mean steady-state C_{max} values of dC and dT following oral administration of doxecitine and doxribtimine in patients with TK2d are well within, and their range similar to, the concentration of circulating endogenous dC and dT reported in non-TK2d

participants. The likelihood of doxecitine and doxribtimine producing QTc prolongation or other cardiac toxicities is low.

Clinical Efficacy and Safety

The efficacy of doxecitine and doxribtimine in the treatment of paediatric and adult patients with TK2d with an age of symptom onset on or before 12 years is confirmed by a significant reduction in the risk of death relative to a matched external untreated cohort. The robust survival benefit is augmented by demonstration of a positive change in disease trajectory in non-survival outcomes relevant for this progressive myopathic disease, namely stabilisation, and in some participants, improvement in developmental motor milestones, as well as use of ventilatory and feeding support following the initiation of treatment. While the survival benefit was driven primarily by participants with an age of TK2d symptom onset ≤2 years, the non-survival outcomes support a treatment benefit in both the subgroup of participants with an age of TK2d symptom onset ≤12 years and the subgroup with an age of TK2d symptom onset >2 and ≤12 years.

The primary determination of the efficacy of doxecitine and doxribtimine in the treatment of patients with TK2d is established in the pooled analysis of MT-1621-101 and TK0102 (referred to as the '**101+102 treated integrated summary of efficacy (ISE) population**') for participants with age of TK2d symptom onset ≤12 years only.

In the 101+102 treated ISE population, 39 participants with an age of TK2d onset ≤12 years were included. Treatment was ongoing for all 39 participants with an age of TK2d symptom onset ≤12 years at the time of data cutoff (15 Mar 2024). Three participants with an age of TK2d symptom onset >12 years discontinued their treatment, 2 due to an AE and 1 due to death. In the 101+102 treated ISE population, the median (first quartile [Q1], third quartile [Q3]) age at TK2d symptom onset was 1.89 years (1.17, 2.69), with 21 participants (53.8%) aged ≤2 years and 18 participants (46.2%) aged between >2 years and ≤12 years at TK2d symptom onset. Median (Q1, Q3) age at first treatment was 4.67 years (2.07, 11.53). The majority of participants were male (26 participants [66.7%]), white (36 participants [92.3%]), and not of Hispanic or Latino ethnicity (25 participants [64.1%]). The most common geographic region of residence was Europe (17 participants [43.6%]). In the 101+102 treated ISE population, participants with an age of TK2d symptom onset ≤12 years (N=39) have a high degree of disease burden: 18 participants (46.2%) were not able to walk assisted or not, 18 participants (46.2%) required ventilatory support and 11 participants (28.2%) required feeding support.

In the matched external untreated cohort (**ISE-MUPD population**), the median (Q1, Q3) age at TK2d symptom onset in this subgroup was 1.33 years (0.75, 2.49), range of 0.00 (1-day old) to 11.00 years. Although motor milestones were not collected for all ISE-MUPD participants, the ISE-MUPD population also showed evidence of disease severity. In the participants with an age of TK2d symptom onset of ≤12 years, 15 of 93 participants (68 participants with missing data) were not ambulatory, 42 of 93 participants (28 participants with missing data) were using ventilatory support, and 8 of 93 participants (67 participants with data not collected) were using feeding support.

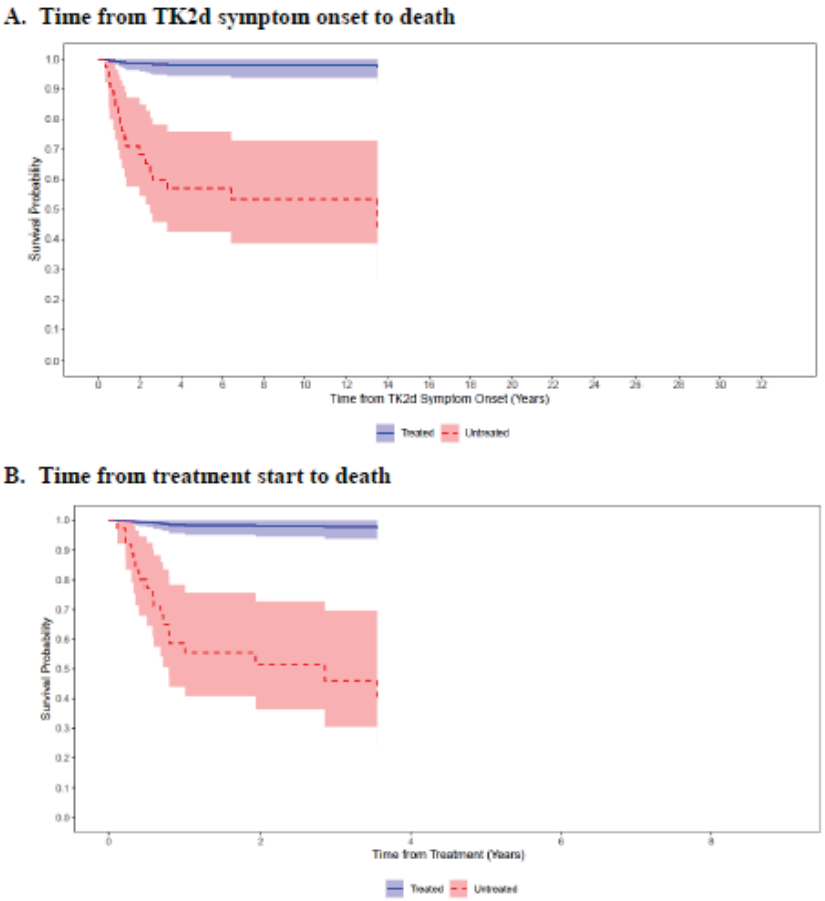
Overall Survival

Survival analyses were performed accounting for age of TK2d symptom onset grouping as a key prognostic factor. Each fitted model accounts for potential confounding from age of TK2d symptom onset group in different ways (matching with stratification, and/or covariate adjustment), and where possible, an attempt has been made to report all results by age of TK2d symptom onset subgroup.

In the 101+102 treated ISE population, no deaths were reported. In the ISE-MUPD untreated population, death was reported in 53 of 93 participants (57.0%).

Treatment resulted in a reduced risk of death for the 101+102 treated ISE population compared with the matching subgroup of untreated participants (ISE-MUPD). The risk of death was reduced by 94% to 97% (hazard ratio [HR]=0.03 to 0.06) for time from TK2d symptom onset and by 95% to 97% (HR=0.03 to 0.05) for time from treatment start.

Figure 1: Treated and untreated matched-pairs (age of TK2d symptom onset ≤12 years)



Note: Marginal model with age of TK2d symptom onset category as strata variable, 50th percentile, no covariate, treatment as time independent variable.

Survival time was improved when looking at both time from symptom onset and time from treatment start, as depicted in Figure 1.

Restricted Mean Survival Time analyses were used to summarise the improvement in survival time with treatment, over pre-specified number of years (30, 20, and 10 years post-symptom onset, and 6, 4, and 2 years post-treatment start). Based on this analysis, treatment with doxecitine and doxribtimine reduced the overall risk of death by approximately 95%. In the 30 years following disease onset, mean survival time was 30 years among treated participants, compared to 13.7 to 15.4 years among untreated participants. Similarly, in the 6 years following treatment start, treated participants experienced a mean survival time of 6 years, compared to 2.9 to 3.4 years among untreated participants.

Non-survival outcomes

Motor milestones

Pre-treatment and post-treatment developmental motor milestone loss and regain for the MT-1621-101 + TK0102 treated population subgroup with an age of TK2d symptom onset ≤12 years are summarised in Table 2.

Prior to initiating treatment, the participants in the MT-1621-101 + TK0102 treated population subgroup with an age of TK2d symptom onset ≤12 years showed a substantial loss of developmental motor milestones with spontaneous regain of a lost milestone in a single patient. A positive change in disease trajectory was observed after starting treatment in the pooled treated population with an age of TK2d symptom onset ≤12 years wherein ongoing loss of developmental motor milestones was substantially reduced relative to the pre-treatment period and a majority of patients regained one or more developmental motor milestones.

Table 7. Developmental Motor Milestones Lost and Regained, Age of TK2d Symptom Onset ≤12 years, MT-1621-101 + TK0102 Evaluable Population

Category	Age of TK2d symptom onset ≤12 years (N=39)			
	Pre-treatment		Post-treatment	
Item	Lost n(%)[a,b]	Regained n(%)[a,b]	Lost n(%)[a,b]	Regained n(%)[a,b]
Ability to hold head upright, unassisted	16/39 (41.0%)	1/38 (2.6%)	0/16 (0.0%)	15/17 (88.2%)
Ability to sit upright, unassisted	13/38 (34.2%)	1/35 (2.9%)	0/13 (0.0%)	10/14 (71.4%)
Ability to stand, assisted	13/36 (36.1%)	3/31 (9.7%)	0/13 (0.0%)	8/15 (53.3%)
Ability to stand, unassisted	14/34 (41.2%)	4/29 (13.8%)	0/14 (0.0%)	7/15 (46.7%)
Ability to walk, assisted	15/36 (41.7%)	3/30 (10.0%)	0/15 (0.0%)	9/16 (56.3%)
Ability to walk, unassisted	15/34 (44.1%)	1/27 (3.7%)	0/15 (0.0%)	6/16 (37.5%)
Ability to climb stairs, assisted	18/31 (58.1%)	2/26 (7.7%)	0/18 (0.0%)	9/19 (47.4%)
Ability to climb stairs, unassisted	16/19 (84.2%)	0/20 (0.0%)	0/16 (0.0%)	6/16 (37.5%)
Ability to run	17/21 (81.0%)	2/20 (10.0%)	1/17 (5.9%)	7/17 (41.2%)

N=number of participants in the total population; n=number of participants in sample; TK2d=thymidine kinase 2 deficiency.

Note:. The last assessment post-treatment was utilised to assign a participant.

[a] *A participant may be counted in more than one motor milestone item, but only once within each line of the table*

[b] *Percentages are based on the number of participants at risk for the specific developmental motor milestone.*

Ventilatory support (invasive or non-invasive)

In the MT-1621-101 + TK0102 treated population with an age of TK2d symptom onset ≤12 years, prior to treatment start, 18/39 (46.2%) participants initiated ventilatory support and no participants discontinued ventilatory support. A positive change in disease trajectory was observed after initiation of treatment: only 4/21 (19.0%) participants in this subgroup started ventilatory support while 5/22 (22.7%) discontinued ventilatory support.

In participants with an age of TK2d symptom onset ≤12 years who were on ventilatory support at treatment start, the number of hours of ventilatory support decreased by ≥4 hours in 5/18 (27.8%) participants in this subgroup after initiation of treatment.

Feeding support (use of nasogastric/gastrostomy tube)

In the MT-1621-101 + TK0102 treated population subgroup with an age of TK2d symptom onset ≤12 years, 12/39 (30.8%) participants had a feeding tube prior to initiation of treatment.

A positive change in disease trajectory was observed following initiation of treatment, 4/28 (14.3%) participants initiated feeding support, with 2 of these participants subsequently discontinuing feeding support in the post-treatment observation period.

5.2 Pharmacokinetic properties

The PK properties of doxecitine and doxribtimine have been studied in healthy volunteers, in participants with moderate and severe renal impairment, and in paediatric and adult participants with TK2d.The PK of doxecitine and doxribtimine were characterised by moderate to high intra- and inter-subject variability.

Absorption

Doxecitine and doxribtimine are rapidly absorbed following oral administration. The absolute oral bioavailability of doxecitine and doxribtimine in humans is not known. After oral administration of doxecitine and doxribtimine, mean peak concentrations (C_{max}) of dC and dT are achieved within approximately 1.5 hours (T_{max}). Systemic exposures (baseline-adjusted C_{max} and AUC_{0-t}) following increasing single oral doses of doxecitine and doxribtimine (86.6 mg/kg, 173.4 mg/kg, and 266.6 mg/kg) in healthy volunteers increase in a less than dose proportional manner for dC and in a more than dose proportional manner for dT.

Administration of 266.6 mg/kg doxecitine and doxribtimine with a high-fat, high-calorie meal increased baseline-adjusted C_{max} and AUC_{0-t} by 79% and 137%, respectively, for plasma dC, and by 27% and 74%, respectively, for plasma dT compared with the fasted state, confirming a significant food effect. The high-fat and high-calorie meal tended to prolong the T_{max} of dC and dT.

Distribution

Plasma protein binding of doxecitine and doxribtimine is relatively weak (less than 10% bound).

Metabolism

Deoxycytidine and dT are primarily degraded (catabolised) by cytidine deaminase and thymidine phosphorylase, respectively, to the nucleobases and the 2-deoxy-α-D-ribose 1-phosphate moiety. Intermediate products of dC catabolism are deoxyuridine, uracil and dihydrouracil with the end products β-alanine, ammonia, and cardon dioxide (CO_2). Thymine, the pyrimidine nucleobase of deoxythymidine, is subsequently catabolised to dihydrothymine and ultimately to γ-amino-isobutyric acid and CO2. Doxecitine and doxribtimine are not substrates of known cytochrome P450 enzymes.

Elimination

Mass balance of dC and dT following oral administration of doxecitine and doxribtimine has not been determined. Hepatic and extrahepatic metabolism is considered to be the main pathway for clearance of dC and dT at plasma concentrations relevant to the proposed dose range of doxecitine and doxribtimine.

Urinary excretion of intact dC and dT is exceedingly low (<1% of dose) in healthy volunteers following single oral administration of doxecitine and doxribtimine. Renal elimination of unchanged dC and dT is likely a minor pathway in the proposed dose range.

Special populations

Based on population PK analysis, age (range: 0.9 to 81 years), sex, and race were not significant covariates of variability in the PK of doxecitine and doxribtimine; no dose adjustments for age, sex or race are recommended. In population PK analysis, the relative bioavailability of dT in participants of Hispanic/Latino ethnicity was lower by ~60% compared to “not Hispanic/Latino” participants; ethnicity had no effect on dC exposures. The sample size was too small with large variabilities in the exposure metrics to make a definitive conclusion of the effect of ethnicity, no change in the dosing for patients of Hispanic/Latino ethnicity is recommended.

Renal impairment

In a dedicated clinical study, renal impairment was associated with a substantial increase in systemic exposures (C_{max}, AUC_{0-t}) of dC and dT following a single oral administration of 266.6 mg/kg doxecitine and doxribtimine (133.3 mg/kg doxecitine and 133.3 mg/kg doxribtimine) in adult non-TK2d volunteers with moderate (eGFR between ≥30 and ≤59 mL/min/1.73 m^2) or severe (eGFR ≥15 and ≤29 mL/min/1.73 m^2) renal impairment when compared with matched healthy volunteers with normal renal function. Systemic exposures to dC and dT were characterised by high inter-subject variability. Baseline-adjusted plasma dC AUC_{0-t} was 122% (56.4 vs 25.4ng*hr/mL) and 66% (52.8 vs 31.8ng*hr/mL) higher in participants with moderate and severe renal impairment, respectively, compared with matched healthy study participant control groups. Baseline-adjusted plasma dT AUC_{0-t} was 447% (23.7 vs 4.34ng*hr/mL) and 148% (31.5 vs 12.7ng*hr/mL) higher in participants with moderate and severe renal impairment, respectively, compared with healthy matched participants. Urinary excretion of intact dC and dT is low (<1% of dose) in all groups.

Hepatic impairment

No specific study has been conducted to evaluate the pharmacokinetics of doxecitine and doxribtimine in hepatic impairment. Considering the hepatic and extrahepatic metabolism of dC and dT, plasma concentrations of dC and dT following administration of doxecitine and doxribtimine may be affected in subjects with significant hepatic impairment.

Paediatric population

Paediatric participants with TK2d in the clinical programme were administered doxecitine and doxribtimine with the same dosing regimen as in adults. Systematic differences in exposures to dC and dT were not apparent between paediatric and adult participants when considering interindividual variability and limited number of participants.

5.3 Preclinical safety data

Oral administration of doxecitine or doxribtimine in the repeat-dose toxicity studies in mice, rats, juvenile rats and dogs did not result in any adverse findings at the highest doses evaluated. Chronic toxicity was evaluated in a single species (rats). A 39-week chronic toxicity study in dog is planned.

Doxecitine and doxribtimine was evaluated in a standard battery of genotoxicity studies and is likely non-genotoxic based on the weight of the evidence. Studies with respect to an impurity, alpha hydroxythymidine, are planned.

Carcinogenicity studies have not been conducted. No evidence of tumorigenicity, hyperplasia, preneoplastic lesions, or neoplasia was observed in rats following 26-week repeat-dose administration of doxecitine and doxribtimine. A 26-week carcinogenicity study in transgenic mice is planned.

Doxecitine and doxribtimine was evaluated in a fertility and early embryonic development study in rat, embryofoetal development studies in rat and rabbit, and a juvenile toxicity study in rat. No doxecitine and doxribtimine–related reproductive or developmental toxicities were observed in the clinical exposure range.
A pre- and postnatal study was not conducted, based on lack of findings in these reproductive and developmental toxicity studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silicon dioxide (silica colloidal anhydrous).
Magnesium stearate.

6.2 Incompatibilities

In the absence of compatibility studies, doxecitine and doxribtimine must not be mixed with other medicinal products.

6.3 Shelf life

30 months. The sachets do not require any special storage instructions.

Reconstituted solution
After reconstitution, the solution should be used within 16 hours. If not used within 16 hours, the oral solution should be discarded.

6.4 Special precautions for storage

After reconstitution
The reconstituted solution may be stored in a refrigerator. Do not store above 25°C. Do not freeze.

6.5 Nature and contents of container

The primary package is a laminated foil sachet. The drug product is in immediate contact with a low density polyethylene (LDPE) inner layer. One sachet contains 4g of doxecitine and doxribtimine powder for oral solution (2g of doxecitine and 2g doxribtimine).

At each delivery, patients will be given a supply of doxecitine and doxribtimine to last them until their next delivery (i.e. at Day 1 they will be given a 1-month supply (+ 1 week overage), at Month 1 they will be given up to a 3-month supply (+ 2 week overage), and so forth.

An administration kit is recommended for the preparation and administration of the oral solution. The administration kit is packaged separately and consists of a dosing system and 2 oral syringes. The dosing system consists of a graduated mixing bottle and a graduated dosing cup which serves as a lid. The mixing bottle is used to measure and mix the required quantity of water and doxecitine and doxribtimine sachets. The reconstituted oral solution is administered using the dosing cup and/or the oral syringe.

6.6 Special precautions for disposal and other handling

Preparation
- Prepare doxecitine and doxribtimine oral solution at room temperature.
- Use the mixing bottle and cup (the “dosing system”) provided in the Administration device kit.
- Dissolve the prescribed number of powder sachets with room temperature water.
- Each sachet contains 2 g of doxecitine and 2 g of doxribtimine.
- Use 40 ml of water per sachet.

- Make a one-day supply of oral solution each morning or for a total daily volume exceeding 640 ml for patients weighing >85.0 kg, the solution should be prepared for each individual dose separately.
- Pour the prescribed amount of water into the mixing bottle first. Then add the powder from the sachets.
- Close the mixing bottle with the dosing cup, and turn upside down and back at least 20 times to mix.
- Once prepared, the oral solution should be ingested within 16 hours.
- Before each administration, turn the mixing bottle slowly upside down and back at least 3 times.
- Discard any remainder after the third dose of the day is taken.

Any unused drug product or waste material should be disposed of in accordance with local requirements. Alternatively, a pharmacist can be requested to throw away unused medicines.

7. SCIENTIFIC OPINION HOLDER

UCB Pharma Ltd
208 Bath Road
Slough, Berkshire
SL1 3WE

8. EAMS NUMBER

00039/0004

9. DATE OF SCIENTIFIC OPINION

To be completed by the MHRA

ADDITIONAL INFORMATION

The primary goal of this EAMS is to provide access to doxecitine and doxribtimine.

The schedule for visits for pre-specified assessments will take place from Day 1, Month 1, then every 3 months for 1 year. Then every 6 months thereafter until end of treatment.

There will be optional collection and use of additional data. This will contribute towards better understanding of early real world clinical experience of treatment with doxecitine and doxribtimine. Entry status into the real word data collection component will have no impact on access to doxecitine and doxribtimine. For the optional data collection, patients will consent separately through the informed consent form.

Data collection will be conducted for the purposes of determining eligibility for treatment and ongoing monitoring of patients. A pre-defined schedule of activities provides the details of the different assessments that will take place throughout the EAMS, and the timepoints for each assessment. Data collection will include (but is not limited to):

- Medical history
- TK2d family history and genetic test

- Physical examination
- Clinician and caregiver global impression scales (severity and change) for TK2d in the patient being treated,
- Developmental Motor Milestones of the patient being treated (clinician and caregiver assessed)

Data will be collected using an online platform consisting of the patient access form and drug supply and resupply forms. Specific data will be collected for all patients treated under the EAMS.

Data will be securely and confidentially submitted through the Bionical Emas portal, which is 21 Code of Federal Regulations part 11 compliant. Informed consent, compliant with the applicable jurisdictional legislation and all applicable medical protocols, will be obtained in writing from the patient by the treating physician before submitting any patient identifiable information as part of this EAMS.

Guidance relating to the re-challenge of doxecitine and doxribtimine after meeting liver-related drug discontinuation criteria must be followed. Re-challenge should only be initiated after consultation with the physician and when patient's liver function tests have returned to baseline.

Instructions for Use

Table of contents

Instructions For Use

Important information
These Instructions for Use contains information on how to prepare and take "or give" a one-day supply of KYGEVVI.

Read these Instructions for Use before taking or giving KYGEVVI and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

When you are prescribed KYGEVVI for the first time, you will be provided with the carton(s) of 30 KYGEVVI powder sachets and the Administration device kit (see **Figure A**).

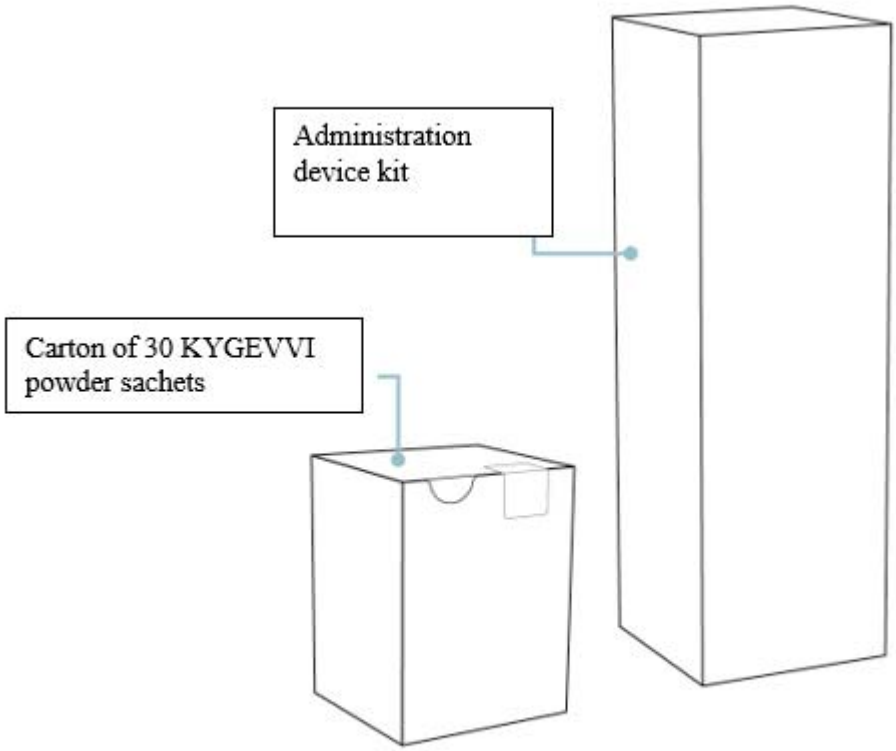
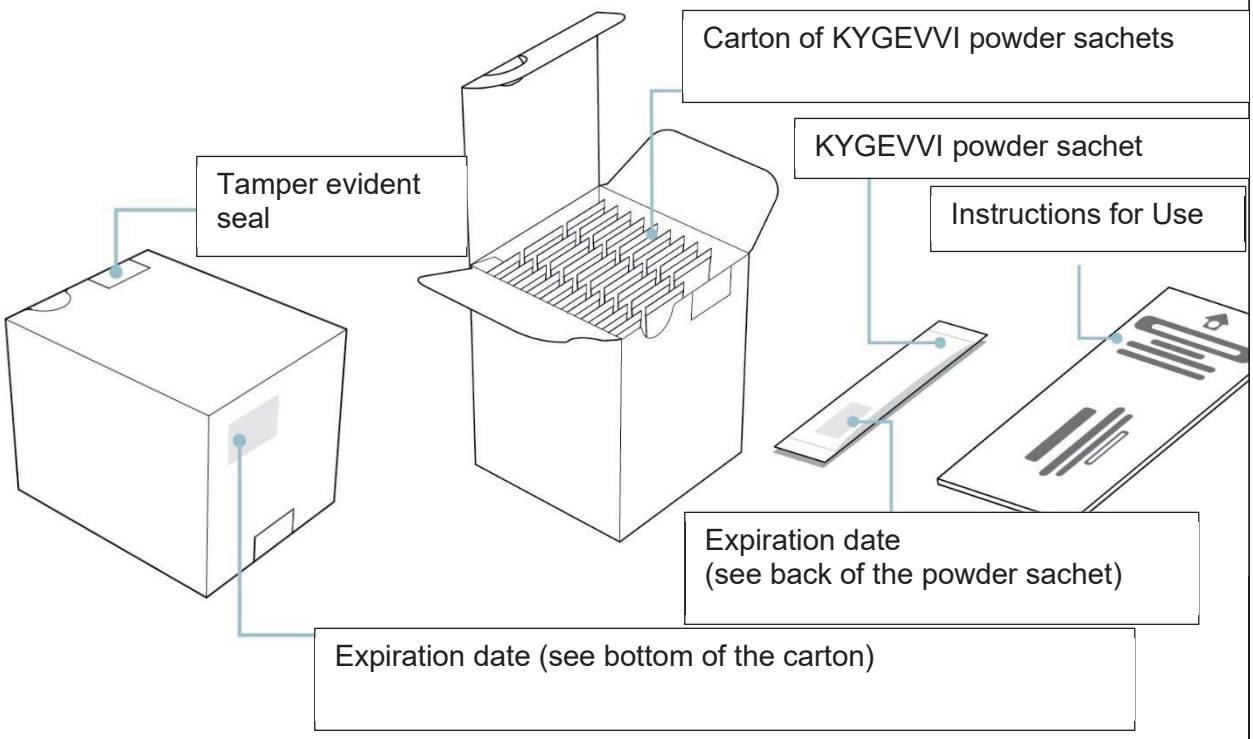


Figure A

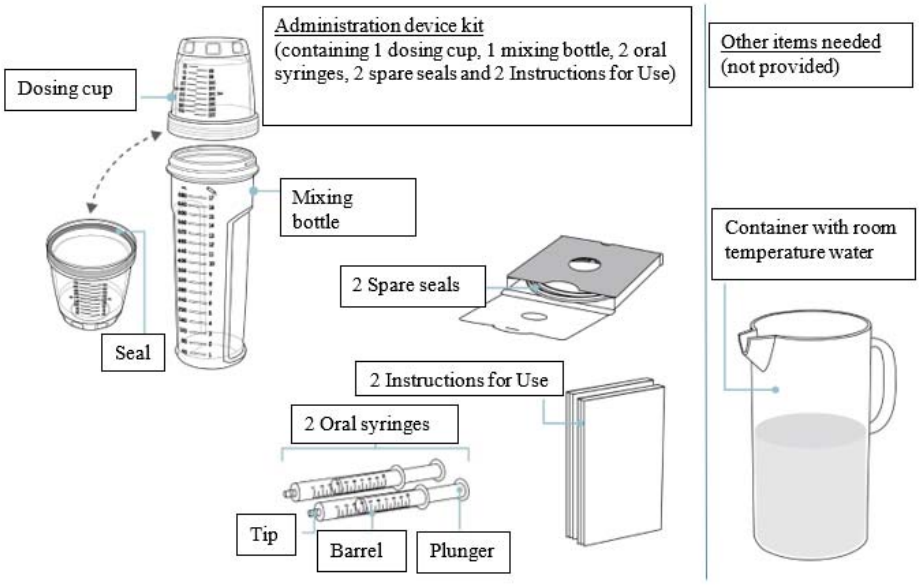
Before you start

Supplies for preparing and taking or giving KYGEVVI
Carton of 30 KYGEVVI powder sachets



Before you start

Supplies for preparing and taking or giving KYGEVVI

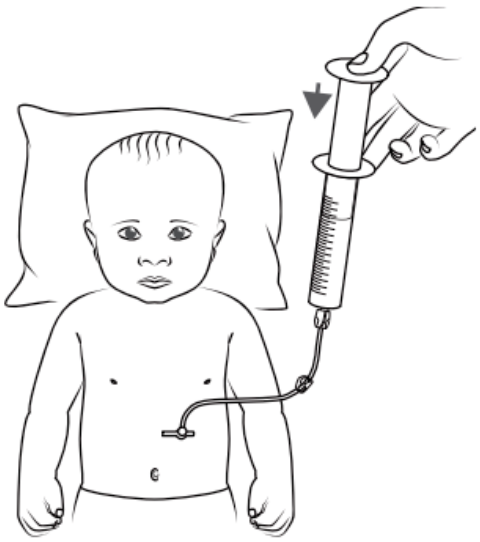


Important information

What you need to know before preparing and taking or giving KYGEVVI

- You will prepare a **one-day supply** of KYGEVVI oral solution to be taken in **3 equal doses** throughout the day (about **6 hours** apart).
- If you or the patient you care for weigh more than 85.0 kg, your doctor may tell you that you need to prepare your 3 daily doses separately. It is important to talk to your doctor about the detailed preparation steps if this is the case.
- KYGEVVI should be prepared and given by adults only.
- Only use the dosing cup, mixing bottle and oral syringes provided with your Administration device kit.
- Each Administration device kit includes two oral syringes. Keep the second oral syringe as a spare.
- Rinse and dry the mixing bottle and dosing cup before first use. **Do not** use the dosing cup, mixing bottle or oral syringe if it appears dirty or damaged.
- Each Administration device kit can be used for 6 months. Contact your healthcare provider when you need a replacement.
- Contact your healthcare provider or pharmacist for a replacement if your mixing bottle, dosing cup, or oral syringe is damaged or if the markings are missing or no longer readable.
- **Do not** use the powder sachets if the tamper evidence seal on the carton is broken.
- Mix KYGEVVI powder only with room temperature water. **Do not** mix KYGEVVI powder with cold or hot water, milk powders or any other liquids or foods. You may have KYGEVVI oral solution left over after taking your 3 individual doses. Throw away (dispose of) any remaining KYGEVVI oral solution at the end of each day.
- If powder spills out of a sachet before use, **do not** use the sachet. Throw it away and use a new KYGEVVI powder sachet.

KYGEVVI oral solution is compatible with most feeding tubes. Follow the steps in this instruction booklet to prepare your one-day supply of KYGEVVI and then follow the feeding tube instructions to give KYGEVVI using a feeding tube.



Preparing your one-day supply of KYGEVVI

Get supplies ready

Step 1

a) Wash your hands well with soap and water.
b) Place the mixing bottle, dosing cup and the oral syringe (if you need one to measure your individual dose) on a clean, well-lit flat work surface. If the dosing cup is attached to the mixing bottle, unscrew it from the mixing bottle and set it down (see **Figure B**).
c) When opening the KYGEVVI carton for the first time, break the tamper evidence seal.
d) Remove the prescribed number of KYGEVVI powder sachets needed for your one-day supply of KYGEVVI out of the carton. Your one-day supply of KYGEVVI will be divided into 3 individual doses.
e) **Do not** open the KYGEVVI powder sachets until Step 2.

Note: The mixing bottle has markings on the front of the bottle in 40 ml increments, each increment is equal to one sachet of medicine.
The dosing cup has markings on the front and back of the cup in 10 ml increments, offset to provide 5 ml increments of measurements.

Figure B

Preparing your one-day supply of KYGEVVI

Measure water and add powder sachets

Step 2

a) On a flat surface, pour the prescribed amount of room temperature water into the mixing bottle (see **Figure C**).
   - **Do not** pour the water into the dosing cup.
   - **Important: Do not** add powder sachets to the mixing bottle before this step.
b) Check to make sure the mixing bottle is filled with water up to the marking that matches the amount prescribed by your healthcare provider. The marking should also match the number of sachets needed for your one-day supply (see **Figure C)**.
c) Check you have counted out the correct number of KYGEVVI powder sachets for your one-day supply, as shown on your prescription.
d) Tap the powder sachet on a hard surface to settle the powder to the bottom of the sachet away from the dotted line (see **Figure D**).

e) Carefully fold and tear or cut along the dotted line (see **Figure E**). If you spill any powder, **do not** use it. Throw the powder sachet away and use a new sachet.
f) Empty the entire powder sachet contents into the mixing bottle containing water. Be careful not to drop the powder sachet into the mixing bottle (see **Figure F**).
g) Pour only 1 powder sachet into the mixing bottle at a time. Repeat **Steps 2d** to **2f**, for each powder sachet until you have poured the prescribed number of powder sachets for your one-day supply.

Figure C

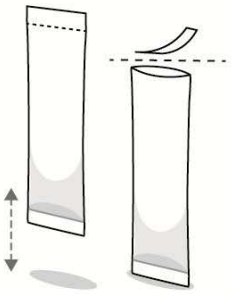


Figure D **Figure E**

Figure F

Preparing your one-day supply of KYGEVVI

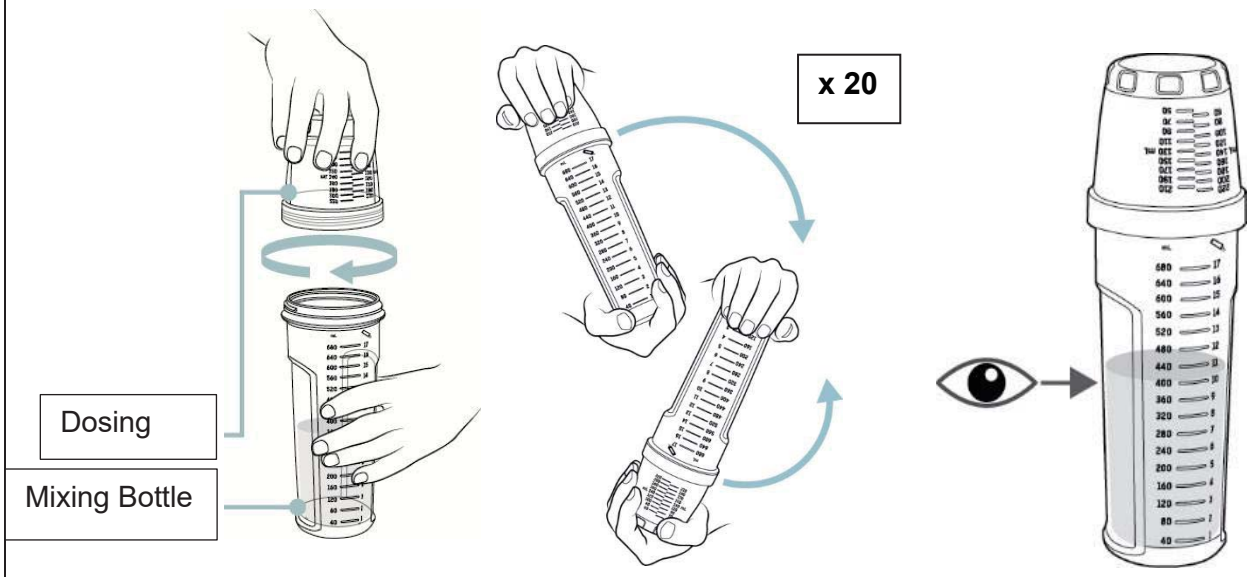
Mix and inspect medicine

Step 3

a) Screw the dosing cup tightly onto the mixing bottle (see **Figure G**).
b) Place one hand at the end of the mixing bottle and the other hand at the end of the dosing cup. Slowly turn the bottle upside down and back. **Repeat at least 20 times** (see **Figure H**).
c) Check the solution. If you see any lumps, keep turning until they disappear (see **Figure I**).
d) The solution will be cloudy and have some powder residue at the bottom or top, this is normal.

You have now prepared your one-day supply of KYGEVVI oral solution for **3 individual doses** or your individual dose if your doctor has told you to prepare your individual doses separately. Take KYGEVVI oral solution with a snack or meal.

Figure G **Figure H** **Figure I**



Dosing methods

How to measure your individual dose

There are 2 different methods to take or give KYGEVVI oral solution depending on your individual dose. Use the table below to identify which steps you should follow:

Doses **equal to** or **greater** than 50 ml	Doses **less** than 50 ml (dosing cup used for dose preparation only)
Example 100 ml  Follow **Step 4**	**Example 14 ml**  Follow **step 5**

Individual doses equal to or greater than 50 ml

Measure and take or give your individual dose

You will need to use the dosing cup to measure and take or give your individual dose.

Step 4. Individual doses equal to or greater than 50 ml

a) Check to ensure the dosing cup is closed tightly onto the mixing bottle and mix the already prepared oral solution by slowly turning the mixing bottle upside down and back at least 3 times.
b) Unscrew the dosing cup from the mixing bottle and place on a flat surface.
c) Pour KYGEVVI oral solution from the mixing bottle into the dosing cup until it reaches the marking on the dosing cup for your prescribed individual dose (see **Figure J**). **Note:** Your dose may be different than the dose shown in Figure J.
d) Drink or give the entire oral solution from the dosing cup (see **Figure K**).
e) When it is time for the **second or third individual dose**, repeat **Steps 4a** to **4d** for each individual dose.
f) After the **first or second individual dose**, go to **Step 6** for instructions on how to clean your supplies and store KYGEVVI oral solution. After the **third individual dose**, go to **Step 7** for instructions on how to clean your supplies and dispose of KYGEVVI oral solution.

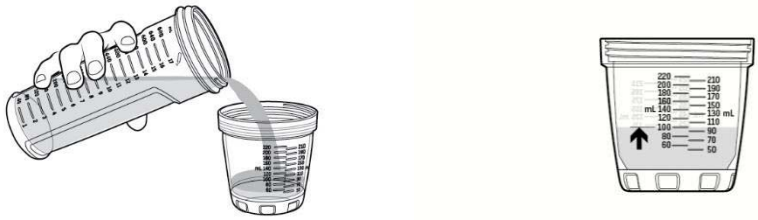


Figure J

Figure K

Individual doses less than 50 ml

Measure and take or give your individual dose
Step 5 – Individual doses less than 50 ml

You will need to use the dosing cup and oral syringe to measure and take or give your individual dose

a) Mix the already prepared oral solution by slowly turning the mixing bottle upside down and back at least 3 times.

b) Unscrew the dosing cup from the mixing bottle and place on a flat surface.
c) Pour slightly more than the amount of oral solution needed for your prescribed individual dose into the dosing cup (see **Figure L**).
d) Push the plunger of the oral syringe all the way down to make sure there is no air in the oral syringe when measuring the dose (see **Figure M**).

If you are giving the oral solution to young children, they must be seated and held in place to avoid the risk of oral solution going down the wrong pipe or choking.

e) Place the tip of the oral syringe into the dosing cup with the oral solution. Fill the oral syringe by pulling the plunger back until it reaches the marking on the oral syringe that matches your prescribed individual dose (see **Figure N**). **Step 5e** may need to be repeated depending on your individual dose.

Figure L

Figure N

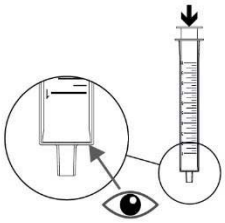


Figure M

f) Place the tip of the oral syringe into the mouth and point the tip towards the inside of either cheek (see **Figure O**).
g) Slowly push the plunger all the way down until the oral syringe is empty (see **Figure O**).

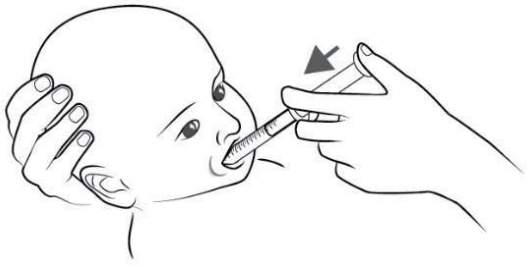


Figure O

h) If your prescribed dose is more than 10 ml, repeat **Steps 5d** to **5g** until you take or give the full individual dose.

i) Pour back any remaining oral solution from the dosing cup into the mixing bottle.
j) When it is time for the **second or third individual dose**, repeat **Steps 5a** to **5i** for each individual dose.
k) After the **first or second individual dose**, go to **Step 6** for instructions on how to clean your supplies and store KYGEVVI. After the **third individual dose**, go to **Step 7** for instructions on how to clean your supplies and dispose of KYGEVVI.

Between individual doses
Clean up after first and second individual dose

Step 6.
After you complete the first or second individual dose:

- Rinse the dosing cup with cold water after each use (see **Figure P**).
- Dry the dosing cup with a clean, dry towel.
- After the dosing cup is dry, screw the dosing cup tightly onto the mixing bottle (see **Figure Q**) and store it at room temperature or in the refrigerator until it is time for the next individual dose.
    - If you used the oral syringe, clean it with cold water:
        - Rinse the oral syringe with cold water by filling the oral syringe with water and pushing it back out (see **Figure R)**. Then remove the plunger from the barrel and rinse the plunger and barrel (see **Figure R)** under running tap water until it is clean.
        - Let the oral syringe barrel and plunger dry in the open air. After the oral syringe barrel and plunger are dry, put the plunger back into the barrel.
    - **Do not** wash the dosing cup or oral syringe in the dishwasher.

Figure P

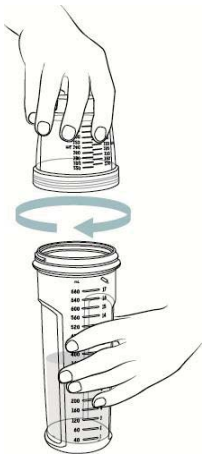


Figure Q

Figure R

End-of-day clean up

Pour out and clean up after third individual dose

Step 7
After you take or give the third individual dose, throw away any remaining KYGEVVI oral solution in the sink.
Do not save KYGEVVI oral solution for another day.

- Remove the seal from the dosing cup to thoroughly clean it (see **Figure S**).
- Clean the mixing bottle, dosing cup and seal by hand with soap and warm water. Use a brush to remove any residue left in the mixing bottle or dosing cup (see **Figure T**).
- Dry the mixing bottle, dosing cup and seal with a clean towel. Put the dry seal back into the dosing cup, with the **thin side of the seal** facing the groove.
- If you used the oral syringe, clean it with cold water:
    - Rinse the oral syringe with cold water by filling the oral syringe with water and pushing it back out (see **Figure U**). Then remove the plunger from the barrel and rinse the plunger and barrel under running tap water until it is clean (see **Figure U)**.
    - Let the oral syringe barrel and plunger dry in the open air. After the oral syringe barrel and plunger are dry, put the plunger back into the barrel.
- **Do not** wash the mixing bottle, dosing cup, seal or oral syringe in the dishwasher.
- Store all supplies in a clean, dry area out of the reach of children for the next day's use.

Figure S

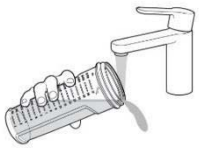


Figure T

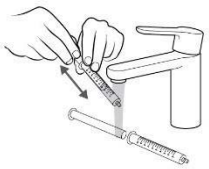


Figure U

Dosing cup maintenance

Replacing the seal if misplaced or damaged

Changing the dosing cup seal

If you misplace the dosing cup seal or you notice leakage when the mixing bottle and dosing cup are tightly closed, change the seal using one of the two spare seals provided in the Administration device kit. Follow these steps to replace the seal:

- Remove the seal in the dosing cup (see **Figure V**). Skip this step if you misplaced the seal.
- Wash the dosing cup groove with warm water (see **Figure W**).
- Get a new seal from the spare seal box (see **Figure X**).
- Insert the seal into the groove of the dosing cup with the **thin side of the seal** facing the groove (see **Figure Y**).

Figure V

Figure W

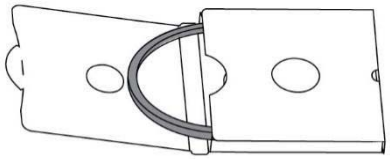


Figure X

Figure Y

Contact your healthcare provider or pharmacist if you have any questions about these Instructions for Use.

DOXECITINE AND DOXRIBTIMINE DOSING QUICK REFERENCE CARD

to be completed by your doctor or authorized health care practitioner

This card provides at-a-glance dosing information about your doxecitine and doxribtimine treatment. Keep it nearby and refer to it as needed.

Patient Name:

Date:

Physician Name:

Physician/Hospital Contact Number:

PREPARE ONE DAILY DOSE

Based on your weight of _____ kg, your doctor has determined you should mix the oral solution as prescribed below to prepare your daily dose.

	IN		PREPARES	
NUMBER of SACHETS		mL of ROOM TEMPERATURE WATER		mL of SOLUTION

ADMINISTER THREE INDIVIDUAL DOSES

_____ml	_____ml	_____ml
morning	**afternoon**	**evening/night**

Take your prescribed individual dose of doxecitine and doxribtimine 3 times a day in equally divided doses, approximately 6 hours apart ±2 hours,

You should take doxecitine and doxribtimine with food.

For NHS England only - additional requirement for registering a patient: N/A

CONTACT INFORMATION

AE reporting: Any AEs or SAEs must be reported to GLOBALICSR@ucb.com within 1 business day.

General medical information: UCB Cares (UCBCares.UK@ucb.com).

EAMS related questions: accessplus@ucb.com