Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scientific Opinion - Public Assessment Report	
Product	Doxecitine and Doxribtimine
EAMS indication	Treatment for children and adults with TK2 deficiency (TK2d), a rare inherited condition, whose symptoms first appeared at 12 years of age or younger.
Company	UCB Pharma Ltd.
EAMS number	EAMS 00039/0004
EAMS Scientific Opinion date	02/07/2026

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 MHRA scientific opinion provides benefit and risk information to physicians who may wish to prescribe the EAMS medicine under their own responsibility. More information about the scheme can be found here:
http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

The scientific opinion is based on assessment of the information supplied to the MHRA on the benefits and risks of the 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, nor should it be regarded as an authorisation to sell or supply such a medicine. A positive scientific opinion is not a recommendation for use of the medicine and should not be interpreted as such. Under EAMS the risk and legal responsibility for prescribing a 'special' remains with the physician, and the opinion and EAMS documentation published by the MHRA are intended only to inform physicians' decision making and not to recommend use. An EAMS scientific opinion does not affect the civil liability of the manufacturer or any physician in relation to the product.

The General Medical Council's guidance on prescribing unlicensed medicines can be found here:
https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

What is Doxecitine and Doxribtimine?
Doxecitine and Doxribtimine are two active medicines that are given together as a powder which is mixed with water to make an oral solution (a liquid medicine that can be swallowed).

What is Doxecitine and Doxribtimine used to treat/diagnoses/prevent?
They are being developed for the treatment of thymidine kinase 2 deficiency (TK2d), a very rare inherited disease that affects the body's ability to produce energy in muscles. The EAMS indication covers children and adults whose symptoms started at 12 years of age or younger.

How is Doxecitine and Doxribtimine used?
Doxecitine and Doxribtimine treatment should be started and supervised by a doctor who has experience managing this disease. Before treatment begins, the doctor will review medical history and perform tests, including blood tests. During treatment, regular monitoring is required, especially of

liver function, because liver test abnormalities can occur. Patients should also report any new symptoms or side effects to their healthcare team promptly.
Doxecitine and Doxribtimine is supplied as a powder in sachets. The powder is mixed with water to make an oral solution (liquid medicine). The daily amount is prepared once each day and then divided into three equal doses, which are taken by mouth about 6 hours apart and always with food. If necessary, the medicine can also be given through a feeding tube. For most patients, a daily supply is prepared once daily and can be stored at room temperature or in a refrigerator for up to 16 hours. Any remaining solution must be discarded at the end of the day. Patients weighing more than 85 kg may be instructed to prepare individual doses separately.
The dose is based on the patient's body weight. The recommended starting dose is 130 mg of doxecitine and 130 mg of doxribtimine per kilogram of body weight per day. The doctor may adjust the dose depending on how well the medicine is tolerated and as the patient's weight changes. Patients and carers are provided with detailed instructions and dosing tables showing exactly how much medicine to prepare and take.
Doxecitine and Doxribtimine contains two active ingredients that are always used together as a combination treatment. Patients should tell their doctor about all other medicines they are taking. Some medicines, including certain antiviral medicines and cancer treatments. Other experimental treatments for TK2 deficiency, including non-approved versions of doxecitine and doxribtimine, should not be used while participating in the EAMS programme.
Patients should attend all scheduled appointments, follow the preparation instructions carefully, and report any side effects, particularly stomach-related symptoms such as diarrhoea, vomiting, or abdominal pain. Regular monitoring helps ensure that the treatment continues to be safe and beneficial.

How does Doxecitine and Doxribtimine work?
Doxecitine and doxribtimine help replace important natural substances that the body needs to make mitochondrial DNA. By helping restore mitochondrial DNA levels, the treatment aims to improve the ability of muscle cells to produce energy and reduce the impact of TK2 deficiency.

How has Doxecitine and Doxribtimine been studied?
Doxecitine and Doxribtimine has been studied in a small clinical development programme for people with thymidine kinase 2 deficiency (TK2d), a very rare inherited mitochondrial disease that mainly affects muscles, breathing and feeding. The EAMS population is focused on children and adults with genetically confirmed TK2d whose symptoms started at or before 12 years of age. The product is described as a powder for oral solution containing 2 g doxecitine and 2 g doxribtimine in each sachet. Because TK2d is extremely rare and serious, the evidence package includes one main ongoing prospective study, retrospective studies, compassionate-use/expanded-access data, and comparisons with untreated patients identified from published literature and chart review. The clinical assessment notes that the primary demonstration of efficacy was based mainly on pooled data from MT-1621-101 and TK0102/MT-1621-102, compared with an external untreated control group.

Main study: TK0102 / MT-1621-102
The main prospective study was TK0102 / MT-1621-102, an ongoing Phase 2, open-label continuation study. This means that all participants received the medicine and both doctors and patients knew that treatment was being given; there was no placebo group. Participants either had previously received pyrimidine nucleoside or nucleotide treatment in earlier programmes, or were newly enrolled with enough information available from before treatment to assess their disease course.
Patients in this study had confirmed TK2 mutations, and the study included patients across a wide age range, from infants to adults. The study was conducted across 7 centres in the United States, Spain and Israel.
The medicine was given as a 1:1 mixture of deoxycytidine and deoxythymidine, corresponding to doxecitine and doxribtimine, at daily doses of 260 mg/kg/day, 520 mg/kg/day or 800 mg/kg/day, depending on the patient’s previous dose. The treatment was given in three equally divided doses per day, about 6 hours apart, either by mouth or through a nasogastric or gastrostomy tube. After Protocol Amendment 3.0, the medicine had to be taken with food.

The main aim of TK0102 was to assess the safety and tolerability of continuing treatment. The study also assessed whether treatment continued to help patients in terms of motor milestones, motor function, breathing support, feeding support, growth and quality of life.
The clinical assessment explains that there was no formal sample size calculation, no randomisation, and no blinding. Data were mainly summarised descriptively, without formal hypothesis testing. This is an important limitation, but the approach was considered understandable given the ultra-rare nature of TK2d.

Measures of effectiveness in TK0102
The effectiveness measures included:
Motor milestones, such as whether patients gained, maintained or lost developmental abilities.
Motor function tests, including the 6-Minute Walk Test, North Star Ambulatory Assessment, Hammersmith Functional Motor Scale Expanded, Revised Upper Limb Module, Egen Klassifikation, CHOP-INTEND and timed walk/run tests.
Respiratory outcomes, including use of ventilatory support and hours of ventilation per day.
Feeding and nutrition outcomes, including feeding tube use and supplemental nutrition.
Growth, including height, weight, BMI and Z-scores.
Quality of life, including patient and clinician global impression scales and other quality-of-life tools.

In TK0102, patients generally maintained previously achieved motor milestones, and some, especially younger patients, gained new milestones. Motor function measures were generally stable or improved, ventilatory and feeding support were mostly stable, and quality-of-life measures suggested stability or improvement.
The assessor concluded that TK0102 provided meaningful longitudinal evidence in a severe ultra-rare disease, but also noted important limitations: the study was open-label, non-randomised, lacked a placebo or internal untreated control group, and included patients who had already received prior treatment, making it harder to understand the effect from a true untreated baseline.

Supportive study: MT-1621-101
MT-1621-101 was a retrospective multicentre chart review, meaning that information was collected from existing medical records rather than from a prospective treatment trial. It included 38 treated participants with genetically confirmed TK2 mutations who had previously taken pyrimidine nucleoside/nucleotide therapy.
The purpose was to describe safety, tolerability and efficacy, and to understand how the disease behaved before and after treatment. Outcomes included survival, motor milestones, motor function, breathing support, feeding support, growth and quality of life.
In this retrospective study, treated participants showed longer survival compared with the historical untreated cohort. Many patients gained new motor milestones or regained previously lost abilities. Motor function, ventilatory support, feeding support, pulmonary function, growth and quality-of-life outcomes generally showed improvement or stabilisation.

Supportive study: MT-1621-107
MT-1621-107 was a Phase 2, non-interventional retrospective chart review. It included both untreated and treated patients with TK2d. Specifically, the study reviewed records from 43 untreated participants and 18 treated participants who had received non-GMP pyrimidine nucleoside/nucleotide therapy and/or doxecitine and doxribtimine outside a company-sponsored study.
This study helped provide a comparison between treated and untreated disease courses. In the treated group, 5 of 18 patients died, while in the untreated group 12 of 43 patients died. The proportion was similar, but the mean and median age at death were much higher in treated patients, suggesting longer survival.
The treated group also showed no further motor milestone loss after starting treatment, and some patients regained lost milestones. In contrast, untreated patients commonly lost milestones and rarely regained them spontaneously. Ventilatory and feeding outcomes also suggested a more stable course in treated patients compared with deterioration in untreated patients.

Expanded access and supplementary datasets

Additional supportive information came from TK0114, an expanded-access/compassionate-use data collection study. This captured patients who received doxecitine and doxribtimine through company-supported expanded access programmes. A total of 43 participants had been enrolled by the data cut-off, and most were receiving 800 mg/kg/day.
Other supplementary studies included TK0110, which collected family-linkage information from patients already included in MT-1621-101, TK0102 and MT-1621-107, and TK0112, which collected additional demographic and family information from untreated patients in the external-control dataset. These studies were supportive rather than primary efficacy studies.

External untreated comparison group
Because it would be difficult and ethically challenging to run a placebo-controlled trial in this rare and severe disease, the applicant created external untreated comparison groups from published case reports, case series and untreated patients from MT-1621-107. The clinical assessment describes an untreated patient database, including the 101-UPD, 101-MUPD, Updated-UPD, ISE-UPD and ISE-MUPD.
The ISE-MUPD was used as the external untreated control group for pooled survival comparisons. The pooled treated group was compared with this untreated group to assess whether treatment improved survival.

EAMS population and main pooled efficacy analysis
The EAMS target population is the subgroup with TK2d symptom onset at or before 12 years of age. In the key pooled treated population from studies MT-1621-101 and TK0102, 39 of 50 participants had symptom onset ≤12 years. In this subgroup, the median age at symptom onset was 1.89 years, and patients had a substantial disease burden: 46.2% were unable to walk, 46.2% required ventilatory support, and 28.2% required feeding support.
In the external untreated comparison population, 93 of 114 participants in the ISE-MUPD had symptom onset ≤12 years. The median age at symptom onset in this untreated subgroup was 1.33 years.

Main measures of effectiveness
The main outcome was survival. In the pooled treated population from MT-1621-101 and TK0102, there were no deaths among the 39 treated participants with symptom onset ≤12 years. In contrast, in the untreated comparison group, 53 of 93 patients died, with a median age at death of 2.64 years. Survival modelling suggested a large reduction in risk of death with treatment. The clinical assessment reports a 94% to 97% reduction in risk of death, depending on the model and whether time was measured from symptom onset or from treatment start.
Restricted mean survival time analyses also supported longer survival. Over 30 years after symptom onset, mean survival time was estimated as 30.0 years in treated patients, compared with 13.7 to 15.4 years in matched untreated patients. Over 6 years after treatment start, mean survival was 6.0 years in treated patients compared with 2.9 to 3.4 years in matched untreated patients.
Other important outcomes included motor milestones, breathing support and feeding support. Before treatment, 32 of 39 patients in the treated pooled population had lost at least one developmental motor milestone. After treatment, milestone loss was less frequent, and 26 of 31 at-risk participants regained at least one lost milestone.
Breathing and feeding outcomes also suggested stabilisation or improvement. Among patients who had used ventilatory support, some were able to discontinue or reduce support after treatment. Feeding tube outcomes were generally stable, and some patients had feeding tubes removed after treatment.

When should Doxecitine and Doxribtimine not be given?
Doxecitine and Doxribtimine should not be taken by patients who are allergic to any of its ingredients.

What are the benefits and risks of Doxecitine and Doxribtimine?

Benefits

Doxecitine and Doxribtimine was studied in people with genetically confirmed thymidine kinase 2 deficiency (TK2d), a rare and serious inherited disease that can cause progressive muscle weakness, breathing problems, feeding difficulties and early death. The EAMS population is patients whose TK2d symptoms started at or before 12 years of age.

Main benefit: improved survival
The main evidence of benefit came from a pooled analysis of treated patients from studies MT-1621-101 and TK0102, compared with an external untreated group made up of patients from published literature and untreated patients from study MT-1621-107.
In the key treated group, 39 patients had TK2d with symptom onset at or before 12 years of age. In this group, no deaths were reported during the available follow-up. In comparison, in the untreated group, 53 out of 93 patients with symptom onset at or before 12 years of age died (Table 1).

Table 1, Main Benefits Seen with Doxecitine and Doxribtimine in Clinical Studies

Outcome	Patients treated with Doxecitine and Doxribtimine	Untreated comparison group
Number of patients with symptom onset ≤12 years	39	93
Number of deaths	0 out of 39	53 out of 93
Percentage who died	0%	57%

This suggests that patients receiving Doxecitine and Doxribtimine had a substantially better chance of survival than similar untreated patients. The survival analyses estimated that treatment reduced the risk of death by approximately 94% to 97%, depending on the statistical model used.
Another way the benefit was measured was by looking at expected survival time over a fixed period. Over the 30 years after TK2d symptoms began, the estimated average survival time was 30.0 years in treated patients, compared with 13.7 to 15.4 years in matched untreated patients. Over the 6 years after treatment started, the estimated average survival time was 6.0 years in treated patients, compared with 2.9 to 3.4 years in matched untreated patients.
Benefits beyond survival: movement, breathing and feeding
The studies also looked at whether patients' physical abilities stabilised or improved. This is important because TK2d usually gets worse over time without effective treatment.
Before treatment, 32 out of 39 patients in the treated group had lost at least one developmental motor milestone, such as abilities related to head control, sitting, standing, walking, climbing stairs or running. After starting treatment, loss of these abilities became less common, and 26 out of 31 patients at risk regained at least one previously lost motor milestone.
The overall pattern of motor milestones changed from decline before treatment to stability or improvement after treatment. Before treatment, the median net change in motor milestones was–2, meaning patients tended to lose abilities. After treatment, the median net change was +2, meaning patients tended to gain or regain abilities. In addition, 94.9% of treated patients had stable or improved motor milestones after treatment, compared with 30.8% before treatment.
Breathing support also showed clinically meaningful improvement or stabilisation. Before treatment, 18 out of 39 patients used ventilatory support, and none had stopped ventilatory support spontaneously before treatment. After treatment, among patients who used ventilatory support before or after starting treatment, 5 patients discontinued ventilatory support and 6 patients reduced the amount of time they needed ventilatory support.
Feeding support was also assessed. Before treatment, 12 out of 39 patients used a feeding tube. After treatment, feeding support needs were generally stable, and feeding tubes were removed in 4 patients after treatment

Risks
Doxecitine and Doxribtimine can cause side effects. Most side effects reported in clinical studies were mild or moderate and many improved over time or with dose adjustment. However, some side effects may require monitoring by your doctor.

The most commonly reported side effects are listed in Table 2.

Table 2. Most commonly reported side effects

Side effect	What it may mean for patients
Diarrhoea	Loose stools, stomach upset and dehydration if severe or prolonged. This was the most frequently reported treatment-related side effect. It usually occurred early after starting treatment and often improved with time or dose adjustment.
Vomiting	Feeling sick and being sick, which may occasionally lead to dehydration. Most episodes were mild and short-lived.
Abdominal pain (stomach pain)	Pain or discomfort in the stomach or upper abdomen. Most cases were mild to moderate.
Increased liver enzymes (ALT and AST)	Changes in blood tests that may indicate irritation or injury to the liver. Most cases were temporary and improved while treatment continued.

Serious or potentially serious side effects

Liver problems

Abnormal liver blood tests were common. In clinical studies, about 44% of patients experienced liver-related laboratory abnormalities. Most were mild, temporary and did not cause symptoms. However, two patients developed liver enzyme elevations greater than three times the upper limit of normal and stopped treatment. Although no cases of severe liver injury were reported, regular liver monitoring is recommended.

Potential consequences: liver inflammation, need for additional monitoring, dose reduction or stopping treatment.

Severe diarrhoea

Diarrhoea was very common and occasionally caused patients to reduce the dose or discontinue treatment. Most cases were mild or moderate, but persistent diarrhoea can lead to dehydration and weight loss if not managed.

Potential consequences: dehydration, weakness, need for dose adjustment or treatment discontinuation.

Serious illness requiring hospital care

Some patients experienced serious medical events such as pneumonia, respiratory failure, swallowing difficulties (dysphagia) and fractures. These events are common complications of TK2 deficiency itself and were generally not considered related to the medicine.

Potential consequences: hospital admission, worsening disability, need for breathing support, or in severe cases death.

Deaths during clinical studies

Among treated patients, a small number of deaths occurred during the clinical development programme. Investigators considered these deaths to be related to the underlying TK2 deficiency and its complications rather than to Doxecitine and Doxribtimine. Most occurred in patients with advanced disease or after treatment had been stopped.

Table 3 summarises key risks

Table 3. Main Risks and Side Effects of Doxecitine and Doxribtimine

Risk	Frequency	Possible consequences
Diarrhoea	Very common	Dehydration, dose reduction, treatment interruption or discontinuation
Vomiting	Very common	Dehydration and stomach upset
Abdominal pain	Very common	Stomach discomfort or pain
Increased liver enzymes (ALT/AST)	Very common	Need for blood-test monitoring; may require stopping treatment in some patients
Liver injury (potential risk)	Uncommon but important	Possible liver inflammation requiring treatment interruption or discontinuation

Serious complications of TK2 deficiency (e.g. pneumonia, respiratory failure)	Reported during studies	Hospitalisation, need for respiratory support, or death; generally considered related to the disease rather than the medicine

Why has Doxecitine and Doxribtimine been given a positive Early Access to Medicine Scientific opinion?

Thymidine kinase 2 deficiency (TK2d) is a very rare, serious and progressive inherited disease that causes worsening muscle weakness, breathing difficulties, feeding problems and can lead to early death. There are currently no approved medicines that treat the underlying cause of TK2d, and available care is mainly supportive, such as ventilatory support, feeding support and mobility aids.
Doxecitine and Doxribtimine has been given a positive Early Access to Medicines Scientific Opinion because clinical studies suggest that it may provide a meaningful benefit for patients with TK2d whose symptoms started at or before 12 years of age. In the main analysis, none of the 39 treated patients died during follow-up, compared with 53 of 93 untreated patients in a matched comparison group. Treatment was also associated with stabilisation or improvement in important aspects of the disease, including movement, breathing and feeding abilities.
Unlike current supportive care, Doxecitine and Doxribtimine is designed to address the underlying disease process by helping restore mitochondrial DNA levels. Clinical data suggest that treatment may reduce the risk of death, help patients maintain or regain physical abilities and slow the progression of the disease. The benefits observed in studies were considered to outweigh the known and potential risks, which mainly include diarrhoea, vomiting, abdominal pain and changes in liver blood tests that can be monitored during treatment.

What are the uncertainties?

Although the available studies suggest that Doxecitine and Doxribtimine may improve survival and help stabilise or improve important symptoms of TK2 deficiency (TK2d), some uncertainties remain. Most studies were relatively small because TK2d is an extremely rare disease. In addition, the main clinical studies did not include a placebo group and many of the comparisons were made using untreated patients identified from medical records and published reports rather than patients enrolled in the same clinical trial.
There is also limited information on the long-term effects of treatment. Although many patients have received treatment for several years, the total number of patients studied remains small, which means that uncommon side effects may not yet be fully understood. Continued monitoring is needed to better understand the long-term safety profile of Doxecitine and Doxribtimine.
Some of the studies included patients who had already been receiving treatment before entering the clinical studies. This makes it more difficult to determine exactly how much of the observed benefit was due to treatment and how much may have been influenced by previous therapy or other factors.
There is also limited information on the use of Doxecitine and Doxribtimine in certain patient groups, including patients with significant kidney or liver impairment, pregnant women and breastfeeding women. Additional data are needed to better understand the benefits and risks in these populations.
The company that makes Doxecitine and Doxribtimine will provide additional information when it becomes available

Are there on-going clinical studies?

The main ongoing study is TK0102 (formerly MT-1621-102), a Phase 2, multicentre, open-label clinical study. It includes children and adults with genetically confirmed thymidine kinase 2 deficiency (TK2d), including patients whose symptoms started at or before 12 years of age, which is the same population covered by the EAMS indication.

What measures are in place to monitor and manage risks?

A risk management plan has been developed to ensure that doxecitine and doxribtimine is used as safely as possible. Based on this plan, the company that makes doxecitine and doxribtimine must ensure that all healthcare professionals expected to use the medicine, as well as patients, are provided with information on the medicine including the side effects and recommendations for preventing or minimising the impact of side effects. Information will be collected about patients before

they enter the scheme. Healthcare professionals will be asked by the company to report adverse effects experienced by patients receiving doxecitine and doxribtimine through the scheme. These safety data will be reviewed and reported to the MHRA on a regular basis by the company.

Healthcare professionals involved in the management of the scheme will receive specific training from the company prior to commencement of patient treatment.

Other information about Doxecitine and Doxribtimine – see EAMS Treatment Protocol