NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Doxecitine–doxribtimine for treating thymidine kinase 2 deficiency in people of any age ID6484

Draft scope

Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of doxecitine–doxribtimine within its marketing authorisation for treating thymidine kinase 2 deficiency in people of any age .

Background

Thymidine kinase 2 deficiency (TK2D) is a genetic disorder that affects energy producing cells (mitochondria). It is caused by mutations in the TK2 gene, which plays a role in producing and maintaining mitochondrial DNA. When the gene does not function properly, there is a large reduction in the amount of DNA in mitochondria and so mitochondrial cells cannot produce and provide enough energy. This leads to muscle weakness (myopathy), which can cause difficulty breathing, eating and walking. Symptoms can progress until people lose the ability to perform these activities independently.

TK2D symptoms can develop at any point in life (from infancy up to late adulthood) and present differently in each individual.[1] Symptoms can vary in severity, age of onset and how quickly they progress, and differ based on TK2D subtype. There are 3 main subtypes of TK2D:

- Infantile onset – when symptoms of TK2D appear before 1 year of age. This is the most severe TK2D subtype, with a rapid progression of symptoms that often leads to early mortality within the first few years of life. Symptoms can include severe muscle weakness, encephalopathy (a brain dysfunction), difficulty breathing and swallowing.[1,2]

- Childhood onset – when symptoms of TK2D appear between ages 1 and 12 years. If symptoms began before age 13 years but an individual is not diagnosed until adulthood, this is still considered childhood-onset TK2D. Often symptoms are severe but progress slower than infantile-onset TK2D. Individuals with childhood-onset TK2D may live into adolescence or early adulthood. Symptoms can include progressive muscle weakness, difficulty swallowing, respiratory muscle weakness and drooping eyelids.[1,2]

- Late onset – when symptoms develop after age 12 years. Often symptoms are less severe and progress slower. Individuals with late-onset TK2D may live for several decades after symptom onset. Symptoms can include muscle weakness, shortness of breath, hearing loss and difficulty moving the eyes.[1,2]

The prevalence of TK2D is estimated to be approximately 1.64 in 1,000,000 people in the world.[3] The symptoms of TK2D overlap with many other diseases, so there may be people living with TK2D who are undiagnosed or misdiagnosed.[1]

There are currently no licensed targeted treatments for TK2D. TK2D is managed through multidisciplinary supportive care. This may involve working with a range of healthcare professionals including neurologists, pulmonologists, physiotherapists, geneticists, metabolic specialist and dietitians. Supportive care strategies aim to manage symptoms as they present, slow down disease progression and improve quality of life. This can involve using respiratory support, feeding tubes, wheelchairs, physical therapy and dietary supplements such as co-enzyme Q10 (see NICE evidence summary 11 Mitochondrial disorders in children: Co-enzyme Q10).

The technology

Doxecitine–doxribtimine (brand name unknown, UCB Pharma). Doxecitine–doxribtimine does not currently have a marketing authorisation in the UK for people with thymidine kinase 2 deficiency. It has been studied in a single-arm clinical trial in people with a confirmed genetic mutation in the TK2 gene.

Intervention(s)	Doxecitine–doxribtimine
Population(s)	People of any age with thymidine kinase 2 deficiency
Subgroups	If evidence allows the following subgroups will be considered: • By TK2D subtype (infantile onset, childhood onset and late onset).
Comparators	Established clinical management without doxecitine–doxribtimine.
Outcomes	The outcome measures to be considered include: • motor function (including, where applicable, age-appropriate motor milestones such as sitting, standing, walking) • bulbar function (including, for example, swallowing and ability to communicate) • respiratory function • body weight and nutritional parameters (including growth) • overall survival • adverse effects of treatment • health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account
Other considerations	Guidance will only be issued in accordance with the marketing authorisation Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations	None.

Questions for consultation

How many people have TK2D in England, and how many would be offered doxecitine–doxribtimine?

What are the subtypes of TK2D? Are there any differences in the cause of TK2D between subtypes, for example, genetic mutations? What is the proportion (or the number) of people in England with each TK2D subtype?

What population would be expected to have doxecitine–doxribtimine? Would doxecitine–doxribtimine be suitable for all people with TK2D? Do you anticipate this treatment to be used in the whole population or for a particular subgroup, for example, by TK2D subtype?

What is considered established clinical management for TK2D? Where do you consider doxecitine–doxribtimine will fit into the existing care pathway for TK2D?

How is TK2D diagnosed? Are the genetic tests to establish the correct diagnosis of TK2D a standard practice in the NHS? If so, what are they?

Is a confirmed genetic mutation in the TK2 gene required before the use of doxecitine–doxribtimine?

Are the outcomes listed appropriate? Are there any other outcomes that should be included in the scope?

Are there any subgroups of people in whom doxecitine–doxribtimine is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Is there any data/evidence available on how long people live with TK2D/the impact of TK2D on quality of life? If so, is this data available by subtype of TK2D (infantile,

childhood or late-onset)? What are the differences in quality and length of life for those with different TK2D subtypes?

Please select from the following, will doxecitine–doxribtimine be:
A. Prescribed in primary care with routine follow-up in primary care
B. Prescribed in secondary care with routine follow-up in primary care
C. Prescribed in secondary care with routine follow-up in secondary care
D. Other (please give details):

Would doxecitine–doxribtimine be a candidate for managed access?

Do you consider that the use of doxecitine–doxribtimine can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which doxecitine–doxribtimine will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.

NICE is considering the evaluation of this technology through its Highly Specialised Technologies Evaluation Programme. We welcome comments on the appropriateness of evaluating this topic through this process. (Information on NICE's health technology evaluation processes is available at: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation).

References

1. Take on TK2d (2024) What is TK2d? Accessed March 2025.

2. National Organization for Rare Disorders (2025) Thymidine Kinase 2 Deficiency. Accessed March 2025.

3. Ma Y, Hines L, Agne M, Chinn C (2023) Prevalence Estimation of Thymidine Kinase 2 Deficiency: An Ultra-Rare Autosomal Recessive Mitochondrial Disease. Value in Health. 26 (12): S229