Appendix B

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

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

Final scope

Final 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 an autosomal recessive 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. Appropriate testing is needed to confirm a diagnosis of TK2D.

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 and speaking, 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]

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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, but do not address the underlying cause of TK2D. These can involve using respiratory support (for example, ventilation or oxygen), nutritional support (for example, feeding tubes), mobility support (for example, wheelchairs and physical therapy) and dietary supplements (for example, 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) • By TK2D severity at baseline (for example, if people are having ventilatory support) • By genotypic subgroup
Comparators	Established clinical management without doxecitine–doxribtimine.

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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 • fatigue • body weight and nutritional parameters (including growth) • neurological function (including, for example, seizures, encephalopathy and cognitive impairment) • overall survival • adverse effects of treatment • health-related quality of life (people with TK2D and carers)
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.

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.

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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