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Health Technology Briefing
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Doxecitine and doxribtimine for treating thymidine kinase 2 deficiency

Company/Developer	UCB Pharma Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 15025	NICE ID: Not available	UKPS ID: 669729

Licensing and Market Availability Plans

Currently in phase III/II clinical trials, with submissions to begin mid 2024.

Summary

Doxecitine and doxribtimine is in development for the treatment of thymidine kinase 2 deficiency (TK2d). Thymidine kinase 2 (TK2) is a protein involved in the normal function of mitochondria. Mitochondria produce energy in the cells of the body. TK2d leads to abnormally low amounts of DNA in mitochondria and because of this defect, the mitochondria are not able to provide the energy that cells need to function properly. This causes severe muscle weakness, along with a host of additional symptoms that may involve breathing, feeding, and walking, and can progress until patients lose many of these abilities, resulting in death. There are no approved pharmacological treatment options for TK2d. Treatment is usually aimed at managing symptoms as they present.

Doxecitine and doxribtimine is a fixed dose combination therapy (two drugs in the same medicine) that targets the underlying causes of TK2d by restoring DNA within the mitochondria. Doxecitine and doxribtimine consists of a combination of deoxynucleosides (the building blocks of mitochondrial DNA) given orally. If licensed, doxecitine and doxribtimine will offer the first disease modifying treatment option for patients with TK2d who currently have no effective therapies available.

Proposed Indication

The treatment of thymidine kinase 2 deficiency (TK2d).[1]

Technology

Description

Doxecitine and doxribtimine (deoxycytidine (dC) and deoxythymidine (dT), MT1621) is a fixed dose combination therapy that targets the underlying pathophysiology of TK2d by restoring mitochondrial DNA (mtDNA) replication fidelity. Doxecitine and doxribtimine consists of a combination of deoxynucleosides (the building blocks of mtDNA) given orally. Deoxynucleoside combination therapy improves nucleotide balance, increases mtDNA copy number, improves cell function, and prolongs life in preclinical models of TK2d.[2] By increasing the levels of thymidine and deoxycytidine in the body, the medicine is expected to make up for the deficiencies in TK2 activity, thereby improving the production of mitochondrial DNA and helping relieve the patient's symptoms.[3]

Doxecitine and doxribtimine is in clinical development for the treatment of TK2d. In the pivotal phase II trial (NCT03845712), doxecitine and doxribtimine is administered orally up to a maximum of 800 mg/kg/day (400 mg/kg/day of dC and 400 mg/kg/day of dT) as tolerated.[1]

Key Innovation

Currently there are no approved therapies for TK2d, and treatment is aimed at managing symptoms as they present.[4] Deoxynucleoside treatment for TK2d has been shown to reverse early onset tetraplegia and enable termination of mechanical ventilation and PEG, halt early onset disease progression and improve muscle weakness, and produce considerable functional improvements in childhood onset patients.[5,6] As doxecitine and doxribtimine is administered orally, there are advantages such as non-invasiveness and convenience of administration.[7]

If licensed, doxecitine and doxribtimine will become the first treatment option for patients with TK2d who currently have no effective therapies available.

Regulatory & Development Status

Doxecitine and doxribtimine does not currently have marketing authorisation in the EU/UK for any indication.

Doxecitine and doxribtimine has the following regulatory designations/awards:

- An orphan drug in the EU in 2017 for TK2d.[3]
- A PRIME status for TK2d by the EMA in November 2018.[8]
- A Breakthrough Therapy by the US FDA for TK2d in February 2019.[9]

Patient Group

Disease Area and Clinical Need

TK2d is an autosomal recessive condition (it can only be passed on to a child if both parents are carriers of the mutated gene) and is considered a mitochondrial DNA depletion/deletions syndrome.[4,10] The gene thymidine kinase 2 (*TK2*) encodes the mitochondrial matrix protein TK2, a critical component of the mitochondrial nucleotide salvage pathway. TK2d causes mtDNA depletion, multiple deletions, or both, which manifest predominantly as mitochondrial myopathy.[5] Ultimately this can lead to a total lack of energy production in tissues in the body, the impact can be worse in cells that require high amounts of energy such as skeletal muscles and in heart muscles.[4] The three main subtypes of TK2d are early onset, childhood-onset, and late-onset. Early onset TK2d has symptom onset before the age of 2 years and rapidly progresses to death, with a median time from symptom onset to death of <2 years.[11,12] Childhood-onset TK2d has symptom onset between age 2 and 12.[13] The estimated median survival for individuals with childhood onset TK2d is 13 years or more.[11] Symptoms of late-onset TK2d begin after age 12 and generally get slowly worse over time. Death usually occurs 20-30 years after the onset of symptoms and is usually due to respiratory failure.[14] Infant/childhood symptoms include respiratory muscle weakness, loss of motor function, progressive muscle weakness, problems swallowing and chewing, hearing loss, and slow mental development. When TK2d presents in late childhood, children may also show signs of droopy eyelids and an inability to move their eyebrows and eyelids. Sadly, for this subgroup TK2d can sometimes be more severe and fatal due to rapidly progressive myopathy and the loss of motor function which can ultimately lead to death due to respiratory failure or respiratory complications. Adult symptoms include muscle weakness, difficulty walking, slowed mental development, trouble breathing and increased risk of seizures and other neurological disfunctions.[4] Due to the rarity of this condition, it is unclear whether it is more common amongst males or females or amongst specific ethnicities.[4] In a 2022 patient listening session, patients and care givers described the disease as “devastatingly progressive,” “relentless,” and “degenerative”.[15]

TK2d is an ultra-rare condition with an estimated prevalence of 1.64 in 1,000,000.[16] As of 2018, approximately 107 molecularly confirmed cases were reported worldwide in published literature, but TK2d incidence is probably underestimated due to early mortality and misdiagnoses.[17] The population likely to be eligible to receive doxecitine and doxribtimine could not be estimated from available published sources.

Recommended Treatment Options

There are no approved pharmacological treatment options for TK2d. Symptomatic treatments that address the manifestations of the disorder can improve an individual’s quality of life.[10]

Trial	NCT03845712, **EudraCT** 2018-004277-27; A Phase 2 Open-Label Study of Continuation Treatment With Combination Pyrimidine Nucleosides in Patients With Thymidine Kinase 2 Deficiency (TK2) **Phase II** – Active, not recruiting **Locations**: Spain, USA, and Israel **Primary completion date**: June 2025
Trial Design	Single group assignment, open label
Population	N=47; subjects with confirmed genetic mutation in the TK2 gene; child, adult, and older adult
Intervention(s)	Oral doxecitine and doxribtimine (maximum of 400 mg/kg/day doxecitine and 400 mg/kg/day doxiribtimine)

Comparator(s)	-
Outcome(s)	Primary outcome measures: - Safety as determined by the number of participants who experience adverse events (AE), type of AE, severity of AE - Number of Participants Who Experience a Clinically Significant Change from Baseline in Clinical Laboratory Tests - Number of Participants Who Experience a Clinically Significant Change from Baseline ECG See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of doxecitine and doxribtimine is not yet known.

Relevant Guidance

NICE Guidance

No relevant guidance identified

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract: Metabolic Disorders (Children). E06/S/b.

Other Guidance

- Mavraki E, Labrum R, Sergeant K, Alston CL, Woodward C, Smith C, et al. Genetic testing for mitochondrial disease: the United Kingdom best practice guidelines. 2023.[18]
- Domínguez-González C, Madruga-Garrido M, Hirano M, Martí I, Martín MA, Munell F, et al. Collaborative model for diagnosis and treatment of very rare diseases: experience in Spain with thymidine kinase 2 deficiency. 2021.[17]
- Parikh S, Goldstein A, Karaa A, Koenig MK, Anselm I, Brunel-Guitton C, et al. Patient care standards for primary mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. 2017.[19]
- NHS Rare Mitochondrial Disorders Service. Care Guidelines. 2017.[20]

Additional Information

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