03 February 2026
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

of an orphan medicinal product submitted for marketing authorisation application

Kygevvi (Thymidine and deoxycytidine)
Treatment of mitochondrial DNA depletion syndrome, myopathic form
EU/3/17/1870

Sponsor: UCB Pharma

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Table of contents

1. Product and administrative information 3

2. Grounds for the COMP opinion 4

3. Review of criteria for orphan designation at the time of marketing authorisation 5

Article 3(1)(a) of Regulation (EC) No 141/2000 5

Article 3(1)(b) of Regulation (EC) No 141/2000 8

4. COMP position adopted on 03 February 2026 9

1. Product and administrative information

Product	
Designated active substance(s)	Thymidine and deoxycytidine
Other name(s)	Kygevvi, Doxecitine, Doxribtimine
International Non-Proprietary Name	Doxecitine/doxribtimine
Tradename	Kygevvi
Orphan condition	Treatment of mitochondrial DNA depletion syndrome, myopathic form
Sponsor's details:	UCB Pharma Allee De La Recherche 60 1070 Anderlecht Belgium
Orphan medicinal product designation procedural history	
Sponsor/applicant	Vall d'Hebron Institute of Research
COMP opinion	15 March 2017
EC decision	20 April 2017
EC registration number	EU/3/17/1870
Post-designation procedural history	
Transfers of sponsorship	Transfer from Vall d'Hebron Institute of Research to Zogenix ROI Limited – EC decision of 03 August 2018 Transfer from Zogenix ROI Limited to Pharma Gateway AB – EC decision of 03 February 2022 Transfer from Pharma Gateway AB to UCB Pharma – EC decision of 21 April 2023
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Peter Mol / Ewa Balkowiec Iskra
Applicant	UCB Pharma
Application submission	06 November 2024
Procedure start	28 November 2024
Procedure number	EMA/H/C/005119/0000
Invented name	Kygevvi

Proposed therapeutic indication	Thymidine Kinase 2 Deficiency (a myopathic form of mitochondrial DNA depletion syndrome) Updated 14/11/2022: Treatment of adult and paediatric patients with thymidine kinase 2 (TK2) deficiency Update 23/10/2023: Treatment of paediatric and adult patients with thymidine kinase 2 deficiency (TK2d) with an age of symptom onset on or before 12 years. Further information on Kygevvi can be found in the European public assessment report (EPAR) on the Agency's website : https://www.ema.europa.eu/en/medicines/human/EPAR/Kygevvi
CHMP opinion	29 January 2026
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Elisabeth Johanne Rook / Vallo Tillmann
Sponsor's report submission	03 February 2025
COMP discussion	20-22 January 2026
COMP opinion (adoption via written procedure)	03 February 2026

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2017 designation was based on the following grounds:

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing thymidine and deoxycytidine was considered justified based on non-clinical data in disease models demonstrating improved survival;
- the condition is life-threatening due to muscle wasting leading to respiratory failure and chronically debilitating due to generalised hypotonia, proximal muscle weakness, loss of motor skills, poor feeding, fatigue and respiratory difficulties;
- the condition was estimated to be affecting less than 0.01 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing thymidine and deoxycytidine as an orphan medicinal product for the orphan indication: treatment of mitochondrial DNA depletion syndrome, myopathic form.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

The orphan condition is "treatment of mitochondrial DNA depletion syndrome, myopathic form".

Mitochondrial DNA Depletion and Deletion Syndrome (MDDS) encompasses clinically and genetically heterogeneous disorders associated with reduction of mtDNA copy number in tissues, leading to insufficient synthesis of mitochondrial respiratory chain enzyme (RCE) complexes and ultimately reduced cellular energy production (Hirano et al, 2001; Berardo et al, 2022).

Mitochondrial DNA Depletion Syndrome (MDS) is classified into subtypes based on the primary organ involvement and clinical presentation, each linked to specific gene defects affecting mtDNA maintenance. MDS is usually classified as myopathic, encephalomyopathic, hepatocerebral or neurogastrointestinal. MDS, myopathic form is caused by mutations in the nuclear *TK2* gene and usually presents before the age of 12 years with progressive proximal muscle weakness, and non-achievement or loss of gross motor function milestones. Diagnosis is confirmed by genetic testing.

The *TK2* gene encodes Thymidine kinase 2 (TK2) which is a mitochondrial matrix protein that phosphorylates thymidine and deoxycytidine pyrimidine nucleosides to generate deoxythymidine monophosphate (dTMP) and deoxycytidine monophosphate (dCMP), which in turn, are converted to deoxyribonucleoside triphosphates (dNTPs) required for mitochondrial DNA (mtDNA) synthesis. Mutations in TK2 impair the mitochondrial nucleoside/nucleotide salvage pathways required for synthesis of deoxyribonucleoside triphosphate (dNTP).

In the literature "Mitochondrial DNA Depletion Syndrome (MDS), myopathic form" and "Thymidine Kinase 2 deficiency (TK2d)" represent the same clinical condition and the terms are used interchangeably.

The approved therapeutic indication "*KYGEVVI is indicated for the treatment of paediatric and adult patients with genetically confirmed thymidine kinase 2 deficiency (TK2d) with an age of symptom onset on or before 12 years"* falls within the scope of the designated orphan condition "Treatment of mitochondrial DNA depletion syndrome, myopathic form."

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

Thymidine kinase 2 deficiency is an ultra-rare, progressive, and devastating disease with very high mortality rates and significant morbidities (Garone et al, 2018; Wang et al, 2018). There are no approved treatments for TK2d, and the standard of care is a palliative approach, with ventilatory and/or feeding support as needed (Dominguez-Gonzalez et al, 2019; Garone et al, 2018; Saada et al, 2001). Given the current standard of care, including lack of a therapeutic intervention, there is significant unmet medical need to address the inherent morbidity and mortality associated with TK2d.

Across all age groups, the symptoms of TK2d are predominantly neuromuscular, and proximal muscle weakness appears to be a common early sign of disease in all patients (Garone et al, 2018). In all patients, the disease involves progressive muscle weakness that manifests with variable rates of progression and functional impairment. The majority (>80%) of patients with TK2d have an age of symptom onset in childhood before the age of 12 years (Wang et al, 2018; Garone et al, 2018). Age of TK2d symptom onset has been shown to be the only factor associated with disease progression (Garone et al, 2018; Wang et al, 2018). In addition to neuromuscular symptoms, patients have commonly reported respiratory difficulties, which can often result in a need for mechanical ventilation, and feeding problems (e.g., dysphagia) with the need for feeding tubes (nasogastric/gastrotomy) in some patients (Garone et al, 2018; Wang et al, 2018; Domínguez-González et al, 2019). Central or peripheral nervous system manifestations including seizure, encephalopathy, cognitive impairment, hearing loss, and polyneuropathy have also been reported but are much less common (Mancuso et al, 2002; Lesko et al, 2010; Oskoui et al, 2006; Gotz et al, 2008; Marti et al, 2010). The impact of TK2d severely compromises patient quality of life, as well as the quality of life of patients' families. It inhibits their ability to participate in normal activities as compared to peers, including loss of functional independence with activities of daily living. Most patients require caregiver support (Amtmann et al, 2023).

There is significant mortality in patients with TK2d. When surveying the literature, two reviews published in 2018 (Garone et al, 2018; Wang et al, 2018) include a largely overlapping group of patients reported as well as unique cases (not previously published). From the publication by Wang et al, 2018, 54% (38/70) patients died due to their disease; the average age of death was 40 months, and the median was 22 months (Wang et al, 2018). Analyses of mortality data from Garone (2018) demonstrated that the median post-onset survival was 1.0 year (confidence interval [CI] 0.58 to 2.33 years) for patients aged ≤1 year of age and 23 years (CI 10.0 to incomputable) for patients aged >1 year of age (Garone et al, 2018); 27.2% of patients died from respiratory failure (Garone et al, 2018). In 18 late-onset patients, defined as onset of symptoms >12 years identified by Domínguez-González, 4 patients (22%) died of respiratory insufficiency at a mean age of 56 years old (Domínguez-González et al, 2019).

In conclusion, the COMP previously considered that the proposed condition is life-threatening due to muscle wasting leading to respiratory failure and chronically debilitating due to generalised hypotonia, proximal muscle weakness, loss of motor skills, poor feeding, fatigue and respiratory difficulties. This position is maintained by the COMP.

Number of people affected or at risk

At time of orphan designation in 2017, the COMP accepted a prevalence of less than 0.01 in 10,000 persons in the European Union. This value was an up-rounded value from the sponsors original proposed estimate of 0.004 in 10,000 persons. In their orphan review report the sponsor maintains a prevalence estimate for the proposed condition of below 0.01 in 10,000 and refers to ORPHANET (www.orpha.net).

The sponsor points out that the diagnosis of mitochondrial disorders has been extremely challenging, due to both the wide variability of disease presentation and the difficulty in determining the specific type of MDDS, low disease awareness, and limited access to genomic sequencing (Cohen et al, 2018). As a result, while TK2d is still very rare, the "true" prevalence and fatality rates of TK2d may exceed reported values, as reported patients do not include those who are undiagnosed or misdiagnosed. Overall, existing research on TK2d epidemiology is sparse, and understanding of the disease epidemiology is still evolving. As already mentioned above, "Mitochondrial DNA Depletion Syndrome (MDS), myopathic form" and "Thymidine Kinase 2 deficiency (TK2d)" represent the same clinical condition.

From 2001 through 2017, key opinion leaders in the field identified 107 confirmed cases of TK2d, including 71 cases from previous publications and 36 newly reported cases (Garone et al, 2018; Wang et al 2018). This information has been the basis for the initial prevalence proposal.

To establish the prevalence of TK2d for the purpose of orphan review, the sponsor presents the results from comprehensive literature reviews in 2019, 2021, and 2022. No study that would directly provide a figure of prevalence of TK2d was identified. Because of that, indirect methods were used to estimate the population-based prevalence of TK2d.

An in-depth literature review conducted in 2019 estimated: a) the prevalence of mitochondrial disease (Gorman et al, 2015; Sanderson et al, 2006; Skladal et al, 2003; Applegarth et al, 2000; Chinnery et al, 2000), b) the proportion of MDDS in mitochondrial disease (Rötig and Poulton, 2009; Sarzi et al, 2007), and c) the proportion of TK2d within MDDS (Gorman et al, 2015; Spinazzola et al, 2009; Sarzi et al, 2007; Carrozzo et al, 2003; Mancuso et al, 2002), which yielded an estimated TK2d prevalent population of approximately 1,700 in the United States (US) (5.2 per 1,000,000 population) and 1,700 in the EU4 (France, Germany, Spain, and Italy) and the United Kingdom (UK) (5.3 per 1,000,000 population). This literature search also identified published information on 103 unique patients with TK2d with the majority of patients described in 3 publications (Dominguez-Gonzalez et al, 2019; Garone et al, 2018; Wang et al, 2018). Data from Garone et al, and Wang et al, indicated that most patients with TK2d experienced childhood onset (84% were 0 to 4 years at onset in Wang et al, 2018; 84.4% were 0 to 12 years at onset in Garone et al, 2018). In Dominguez-Gonzalez et al, all patients described had an age of TK2d symptom onset ≥12 years.

The literature review that was conducted in 2021 leveraged methodologies and sources similar to those used in the 2019 literature review, and produced some additional findings. Initial mitochondrial disease prevalence data are sourced from point prevalence estimates based on analyses of diagnosed or identified patients (Gorman et al, 2015; Chinnery, 2015; Yatsuga et al, 2012; Diogo et al, 2009; Schaefer et al, 2008; Castro-Gago et al, 2006; Arpa et al, 2003; Darin et al, 2001; Chinnery et al, 2000). The rates of mtDNA depletion among known mitochondrial disease patients (Rötig and Poulton, 2009; Sarzi et al, 2007; Macmillan and Shoubridge, 1996) and the proportion of patients with mtDNA depletion due to *Tk2* mutation (Bychkov et al, 2021; Spinazzola et al, 2009; Alberio et al, 2007; Sarzi et al, 2007; Carrozzo et al, 2003; Mancuso et al, 2002) were estimates that represent the true frequency of these disorders. Based on these estimates, like in the 2019 literature review, a "funnel" approach was used to narrow down from the initial mitochondrial disease rates to estimates of TK2d prevalence. Overall, data suggested estimated prevalence at approximately 2 to 3.3 per 1,000,000 population in both the US (660 to 1100 patients) and EU4 and the UK (650 to 1,080 patients).

In the literature review conducted in 2022, the method and data sources were largely consistent with the previous work, though several additional sources were identified (Castro-Gago et al, 2006; Yamazaki et al, 2014; Pronicka et al, 2016), and the degree of uncertainty was quantified (Ma et al, 2023). Data suggested a prevalence of 1.64 per 1,000,000 population, which was slightly lower than

estimated in the previous work, driven by excluding the sources with high uncertainty and by greater weighting of the most robust papers.

In conclusion, the sponsor proposes to maintain a prevalence estimate for the condition of below 0.01 in 10,000, in alignment with the value indicated by Orphanet (www.orpha.net). The COMP does not accept prevalence estimates which are based on Orphanet alone, as it is not a primary epidemiologic data source. The committee also noted that the prevalence estimates reported in the literature reviews conducted by the sponsor in 2019, 2021, and 2022 are above 0.01 in 10,000 persons, i.e. 0.053, 0.033 and 0.0164 respectively. The COMP agreed with the sponsor on the remaining uncertainty of the "true" prevalence of the condition owing to issues including scarce epidemiologic data for this condition and likelihood of underdiagnosis.

Therefore, the COMP accepted a higher prevalence estimate of "less than 0.1 in 10,000 persons" instead of the sponsors proposed value of "0.01 in 10,000 persons". Even though this is a 10-fold difference than the value agreed at time of initial orphan designation in 2017, this condition is still considered to be very rare and meeting the designation criterion of below 5 in 10,000 persons.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

There are no approved medicinal products in the European Union (EU) indicated for treatment of the condition.

Management of the condition is limited to supportive care, including ventilatory support and enteral nutrition when needed. Palliative care approaches have remained largely unchanged since TK2d was first recognized as a disease in 2001 (Dominguez-Gonzalez et al, 2019; Garone et al, 2018; Saada et al, 2001).

Significant benefit

Not applicable.

4. COMP position adopted on 03 February 2026

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of mitochondrial DNA depletion syndrome, myopathic form (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be less than 0.1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening due to progressive muscle wasting leading to respiratory failure and chronically debilitating due to generalised hypotonia, proximal muscle weakness, loss of motor function milestones, fatigue and respiratory insufficiency, dysphagia and malnutrition;
- at present, no satisfactory method for the treatment of the condition has been authorised in the European Union for patients affected by the condition.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Kygevvi, thymidine and deoxycytidine, doxecitine/doxribtimine for treatment of mitochondrial DNA depletion syndrome, myopathic form (EU/3/17/1870) is not removed from the Community Register of Orphan Medicinal Products.