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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Emcitate (tiratricol)
Treatment of Allan-Herndon-Dudley syndrome
EU/3/17/1945

Sponsor: Rare Thyroid Therapeutics International AB

Note

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

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1. Product and administrative information

Product	
Designated active substance(s)	Tiratricol
Other name(s)	-
International Non-Proprietary Name	Tiratricol
Tradename	Emicitate
Orphan condition	Treatment of Allan-Herndon-Dudley syndrome
Sponsor's details:	Rare Thyroid Therapeutics International AB Klara Norra Kyrkogata 26 Tr 2 Stockholms Domkyrkofors. 111 22 Stockholm Stockholms Lan Sweden
Orphan medicinal product designation procedural history	
Sponsor/applicant	Medical Need Europe AB
COMP opinion	5 October 2017
EC decision	8 November 2017
EC registration number	EU/3/17/1945
Post-designation procedural history	
Transfer of sponsorship Sponsor's name change	- Transfer from Medical Need Europe AB to MN Development AB – EC decision of 16 May 2018 - Name change from MN Development AB to Rare Thyroid Therapeutics – EC letter of 23 November 2018
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Janet Koenig / Elita Poplavska
Applicant	Rare Thyroid Therapeutics International AB
Application submission	6 October 2023
Procedure start	26 October 2023
Procedure number	EMA/H/C/005220
Invented name	Emcitate
Proposed therapeutic indication	Emcitate is indicated for the treatment of peripheral thyrotoxicosis in patients with MCT8 deficiency (Allan-Herndon-Dudley Syndrome), from birth. Further information can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Emcitate
CHMP opinion	12 December 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Vallo Tillmann / Darius Matusevicius
Sponsor's report submission	20 August 2024
COMP opinion (adoption via written procedure)	13 December 2024

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2017 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 tiratricol was considered justified based on non-clinical data demonstrating a potential effect on hypothyroidism in the central nervous system and clinical data demonstrating successful management of peripheral symptoms of thyrotoxicosis;
- the condition is life-threatening due to a risk of sudden cardiac arrest or aspiration pneumonia and chronically debilitating due to cognitive impairment and infantile hypotonia, which evolves to spastic paraplegia. Other symptoms include symptoms of peripheral hyperthyroidism such as increased heart frequency, tremor, weight loss and muscular weakness;
- 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 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 tiratricol as an orphan medicinal product for the orphan indication: treatment of Allan-Herndon-Dudley syndrome".

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

Allan-Herndon-Dudley syndrome (AHDS, International Classification of Diseases 11th Revision code 5A00.0Y) is a rare, X-linked recessive neurodegenerative disorder caused by mutations in the *SLC16A2* gene, which encodes monocarboxylate transporter 8 (MCT8), a thyroid hormone (TH) transporter critical for the proper cellular uptake of thyroid hormones, particularly triiodothyronine (T3). The condition predominantly affects males, while carrier females may exhibit mild or no symptoms due to

X-inactivation. AHDS is characterized by severe neurodevelopmental impairments and peripheral tissue thyrotoxicosis, resulting in a complex phenotype of both neurological and systemic manifestations.

The pathophysiology of AHDS arises from defective MCT8, leading to impaired transport of T3 into the central nervous system (CNS). The brain, especially during crucial periods of foetal and early postnatal development, depends heavily on thyroid hormone for proper growth and maturation. In the absence of functional MCT8, T3 fails to enter the CNS effectively, causing developmental delays and irreversible structural damage to the brain. Key effects include impaired development of the cortex and cerebellum, delayed neuronal differentiation, altered neurofilament expression, and a lack of parvalbumin-expressing interneurons in the cortex. Additionally, synaptogenesis is disrupted, and myelination is delayed and defective, leading to significant cognitive and motor dysfunction. Most of the hypothyroidism-related brain damage occurs prenatally, with the foetal brain particularly vulnerable during critical stages of development (Bernal 2000, Lopez-Espindola et al. 2014).

In contrast to the CNS, peripheral tissues such as skeletal muscles, bones, and the liver are affected by excessive T3, which accumulates due to the increased activity of type 1 deiodinase (D1). This enzyme converts thyroxine (T4) to T3, leading to elevated serum levels of T3. While the CNS suffers from hypothyroidism, peripheral organs that utilize alternative TH transporters are exposed to excess T3, resulting in tissue-specific thyrotoxicosis. This causes significant metabolic disturbances in various tissues: extensive muscle wasting in skeletal muscles, short stature in bones, and elevated production of hepatic sex hormone-binding globulin (SHBG) in the liver (Liao et al. 2011, Mullur et al. 2014, Visser 2016).

Clinically, AHDS presents in infancy with congenital hypotonia, which typically appears at birth or within the first few months of life. As the condition progresses, spasticity develops, manifesting as muscle contractures, the Babinski sign, and clonus. Hyperreflexia often emerges later. Infants with AHDS also display muscle hypoplasia and generalized muscle weakness, which impair their ability to support their heads and cause delayed motor milestones. These neuromuscular issues are usually noticeable early in life, as affected individuals struggle with basic motor functions such as sitting, standing, and walking. The disease is also marked by global developmental delay, with most individuals unable to achieve significant cognitive or motor milestones.

A hallmark of AHDS is the thyroid dysfunction characterized by elevated serum T3 levels, while T4 and thyroid-stimulating hormone (TSH) levels may remain normal or slightly reduced. The elevated T3 is largely due to the activity of type 1 deiodinase, especially in the liver, leading to excess T3 production. Despite the excess thyroid hormone in the peripheral tissues, the brain remains in a hypothyroid state, resulting in a stark discrepancy between the CNS and peripheral thyroid hormone activity. This dysregulation contributes to the broad range of systemic symptoms, including muscle wasting, short stature, and abnormal hepatic SHBG production.

Diagnosis of AHDS is confirmed through a combination of clinical presentation, biochemical findings, and genetic testing. Clinically, the presence of hypotonia, spasticity, and developmental delay, along with signs of thyrotoxicosis, are suggestive of the syndrome. Biochemical analysis typically reveals elevated T3 levels, often with normal or reduced T4 and TSH levels, indicative of thyroid hormone dysregulation. Genetic testing for mutations in the SLC16A2 gene definitively confirms the diagnosis.

The approved therapeutic indication "treatment of peripheral thyrotoxicosis in patients with monocarboxylate transporter 8 (MCT8) deficiency (Allan-Herndon-Dudley Syndrome), from birth" falls within the scope of the designated orphan condition "treatment of Allan-Herndon-Dudley syndrome".

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

Allan-Herndon-Dudley syndrome (AHDS) is a chronically debilitating and life-threatening condition that disrupts thyroid hormone function beginning in the prenatal period. Affected individuals, typically males with pathogenic mutations in the *SLC16A2* gene, experience severe developmental delays, including an inability to acquire walking or language skills, and most suffer from severe intellectual disability (Lopez-Espindola et al. 2014).

AHDS is characterized by severe hypotonia, which emerges during infancy and results in poor head control, persisting into adulthood. Dysphagia is another common manifestation, often necessitating gastric tube placement to address weight loss and ensure adequate caloric intake. This requirement is further exacerbated by the elevated metabolic demands caused by thyrotoxicosis (Sarret et al. 2020). Patients frequently exhibit dystonic and/or athetoid movements as well as paroxysms of kinesigenic dyskinesias, which are triggered by somatosensory stimuli such as diaper changes, clothing adjustments, or lifting (Brockmann et al. 2005). Additionally, treatment-resistant seizures typically begin in infancy and further complicate management of the disease (Remerand et al. 2019, Sarret et al. 2020).

A recent natural history study involving 151 patients with AHDS reported a median survival of 35 years (95% CI 8.3–61.7), with the primary causes of mortality being pulmonary infections and sudden death (Groeneweg et al. 2020). These findings underscore the severe and progressive nature of the disease, highlighting its significant impact on both quality and duration of life.

In summary, AHDS is a severe, life-threatening disorder marked by profound developmental delay, intractable neuromuscular symptoms, and systemic complications. Its chronic and debilitating nature necessitates comprehensive, multidisciplinary care to optimize outcomes and manage the complex clinical challenges faced by affected individuals and their families.

Number of people affected or at risk

At the time of its initial orphan designation in 2017, the Committee for Orphan Medicinal Products (COMP) estimated that Allan-Herndon-Dudley Syndrome (AHDS) affected fewer than 0.01 per 10,000 persons in the European Union (EU). Since then, the sponsor has refined prevalence estimates using sparse epidemiological data, patient identification networks, and records from patient organizations, reflecting the limited understanding of this disorder.

The Triac I clinical trial conducted by investigators at the Erasmus Medical Center in Rotterdam, which recruited 46 patients from nine countries (eight within the EU and one in South Africa), provided valuable insights into the diagnosed prevalence of AHDS. Across a combined population of 387 million, the trial observed a prevalence of 0.001 per 10,000, indicating that the study cohort represents a substantial proportion of known cases across these regions.

To expand the understanding of prevalence, systematic searches for epidemiological studies on AHDS (or "MCT8 deficiency") were conducted in PubMed in June 2023, yielding 241 publications. Despite the extent of this search, only five studies provided relevant data, and none offered definitive prevalence figures (Grijota-Martínez et al., 2020; Gronenweg et al., 2020a; Kubota et al., 2022; Visser et al., 2013; van Geest et al., 2021).

One pivotal study conducted in the Netherlands sought to identify AHDS prevalence by screening institutionalized males with unexplained intellectual disabilities (ID). This study estimated a prevalence of 0.2 per 10,000 males, equivalent to 0.1 per 10,000 in the general population (Visser et al., 2013). The methodology was grounded in the observation that intellectual disability affects roughly 2% of the general population, with 0.5% experiencing severe forms requiring institutionalization. Among these cases, 10% of males were identified with X-linked mental retardation (XLMR), and 3.9% of XLMR cases were linked to MCT8 mutations, resulting in the reported prevalence estimate.

Supporting this figure, the Erasmus Medical Center in Rotterdam, has diagnosed approximately one Dutch male patient per annual birth cohort, equivalent to a prevalence of 1 per 140,000 (0.07 per 10,000). Global studies further corroborate the extreme rarity of AHDS, with frequencies cited as <1 per 1,000,000 worldwide (Grijota-Martínez et al., 2020) and <1 per 1,890,000 in Japan (Kubota et al., 2022).

Applying a high-end prevalence estimate of 0.2 per 10,000 to the EU population (448.8 million as of 2024), the number of individuals with AHDS was estimated by the sponsor to be around 100 cases in the EU. These figures highlight the rarity of the condition and the significant challenges in accurately identifying and diagnosing affected individuals, given the limited awareness and sparse epidemiological data available. The Committee for Orphan Medicinal Products (COMP) considered the sponsor's prevalence estimates to likely represent an overestimate, given the limited robustness of available data and the inherent difficulties in identifying cases of such a rare and complex condition. Based on these considerations, the COMP concluded that the prevalence of the condition could be considered to be less than 0.1 in 10,000 persons in the European Union.

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

The current management of the disease mainly involves palliative care measures directed at alleviating symptoms, providing adequate nutrition and hydration, and managing complications.

However, no therapy is currently available that can meaningfully alter the disease course of AHDS.

Significant benefit

Not applicable.

4. COMP list of issues

Not applicable.

5. COMP position adopted on 13 December 2024

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 Allan-Herndon-Dudley syndrome (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 a risk of sudden cardiac arrest or aspiration pneumonia and chronically debilitating due to cognitive impairment and hypotonia, which evolves to spastic paraplegia. Other symptoms include peripheral hyperthyroidism with increased heart frequency, tremor, weight loss and muscular weakness;
- 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 Emicitate, tiratricol for treatment of Allan-Herndon-Dudley syndrome (EU/3/17/1945) is not removed from the Community Register of Orphan Medicinal Products.