14 December 2023
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Agamree (vamorolone)
Treatment of Duchenne muscular dystrophy
EU/3/14/1309

Sponsor: Santhera Pharmaceuticals (Deutschland) GmbH

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)	17α,21-dihydroxy-16α-methyl-pregna-1,4,9(11)-triene-3,20-dione
Other name(s)	Anti-inflammatories; Antianaemics; Antiasthmatics; Corticosteroids; Glucocorticoids; Pregnatrienes; Small molecules
International Non-Proprietary Name	Vamorolone
Tradename	Agamree
Orphan condition	Treatment of Duchenne muscular dystrophy
Sponsor's details:	Santhera Pharmaceuticals (Deutschland) GmbH Marie-Curie-Strasse 8 79539 Loerrach Baden-Wuerttemberg Germany
Orphan medicinal product designation procedural history	
Sponsor/applicant	NDA Group AB
COMP opinion	10 July 2014
EC decision	22 August 2014
EC registration number	EU/3/14/1309
Post-designation procedural history	
Transfer of sponsorship	Transfer from NDA Group AB to ReveraGen BioPharma Limited – EC decision of 13 May 2015 2nd transfer from ReveraGen BioPharma Limited to Pharma Gateway AB - EC decision of 11 January 2019 3rd transfer from Pharma Gateway AB to Santhera Pharmaceuticals (Deutschland) GmbH- EC decision of 13 September 2022.
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Martina Weise / Elita Poplavska
Applicant	Santhera Pharmaceuticals (Deutschland) GmbH
Application submission	29 September 2022
Procedure start	27 October 2022
Procedure number	EMA/H/C/005679/0000
Invented name	Agamree
Proposed therapeutic indication	AGAMREE is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients aged 4 years and older. 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/Agamree
CHMP opinion	12 October 2023
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Elisabeth Penninga / Armando Magrelli

Sponsor's report submission	19 May 2023
COMP discussion	3-5 October 2023
COMP opinion (adoption via written procedure)	13 October 2023

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 2014 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 17α,21-dihydroxy-16α-methyl-pregna-1,4,9(11)-triene-3,20-dione was considered justified based on preclinical data showing increased muscle strength in a relevant model of the condition;
- the condition is life-threatening and chronically debilitating due to progressive weakness occurring throughout the proximal musculature affecting the muscles of the hips, thighs, pelvic area and shoulders and eventually affecting all voluntary muscles. This is followed by dilated cardiomyopathy and cardiac output decrease, leading to terminal respiratory or cardiac failure often by late adolescence. Patients rarely live beyond the age of 30 years;
- the condition was estimated to be affecting less than 0.8 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 17α,21-dihydroxy-16α-methyl-pregna-1,4,9(11)-triene-3,20-dione, as an orphan medicinal product for the orphan indication: treatment of Duchenne muscular dystrophy".

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

Duchenne muscular dystrophy (DMD) is a progressive, X-linked recessive, neuromuscular degenerative and fatal disease. It is the most common muscular dystrophy. DM caused by mutations in the dystrophin gene (DYS gene; DMD; locus Xp21.2). Approximately one third of all dystrophin mutations arise from new mutations, and the remaining two-thirds are inherited from a mother who is a carrier of the mutation. The disease primarily affects males. Approximately 10% of female carriers do show disease manifestations, which can include effects on cognitive and/or cardiac function. However, a few cases in female patients do show the same severity as affected males. Affected females with DMD usually have chromosomal rearrangements, and most are assumed to have skewed X-inactivation, which can also cause disease manifestation.

Dystrophin is a cytoskeletal protein, which is part of the Dystrophin-Associated Protein Complex (DAPC) located between the extracellular matrix and inner cytoskeleton of muscle fibres. It stiffens muscle fibres, acting as a type of shock absorber by providing resistance against deformation. Mutations can be frameshifting mutations, deletions, or nonsense mutations that result in either non-functional or missing dystrophin protein from the DAPC and myofibres. Its deficiency leaves the fibres susceptible to contraction-induced microfissures, which disrupt calcium homeostasis, ultimately resulting in cellular necrosis. As the disease progresses, muscle fibres are necrotic and are replaced by fibrotic and adipose tissues. The final muscular atrophy and fibrotic tissues are the result of numerous cycles of degeneration and regeneration.

First symptoms are mostly seen before 5 years of age, most commonly before 3 years of age. Loss of ambulation usually occurs between 7 to 11 years of age. Despite these best efforts, most patients will die before their 4th decade.

The first clinical manifestations of muscle weakness include gait abnormalities and difficulties in climbing stairs and rising from the floor. Progressive pelvic girdle weakness and muscle contractures will further affect ambulation, with subsequent progressive loss of upper limb function. Full-time wheelchair dependency and axial weakness lead to the development of scoliosis and joint contractures in upper and lower limbs. At the advanced stages of the disease, patients have spinal and chest wall deformities. Progressive weakness of respiratory muscles results in a restrictive pulmonary syndrome that evolves into respiratory insufficiency during the late second or third decade. With increasing age,

DMD patients typically develop a progressive dilated cardiomyopathy, eventually leading to symptomatic congestive heart failure and an increased risk of cardiac arrhythmia and sudden death. Without intervention, cardiac involvement and respiratory complications will result in early mortality in the second or third decade.

The approved therapeutic indication "*AGAMREE is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients aged 4 years and older*" falls within the scope of the designated orphan condition "treatment of Duchenne muscular dystrophy".

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

The COMP has previously accepted the condition is life-threatening and chronically debilitating due to progressive weakness occurring throughout the proximal musculature affecting the muscles of the

hips, thighs, pelvic area and shoulders and eventually affecting all voluntary muscles. This is followed by dilated cardiomyopathy and cardiac output decrease, leading to terminal respiratory or cardiac failure often by late adolescence. Patients rarely live beyond the age of 30 years.

This view is still retained by the COMP for this procedure.

Number of people affected or at risk

The sponsor proposes a prevalence estimate of 0.44 in 10,000 male persons in the EU for Duchenne muscular dystrophy (DMD) in Europe. At the time of the original orphan designation (22 August 2014), the prevalence of Duchenne muscular dystrophy (DMD) in Europe was estimated to be 0.85 in 10,000.

For the orphan maintenance report, the sponsor performed a new systematic search of peer-reviewed published literature. No new data of DMD prevalence in Europe was identified by the sponsor as compared to the original orphan application. In the absence of relevant new data on DMD prevalence in Europe, in agreement with EMA/COMP/436/01 guideline of 20 June 2019, the prevalence was calculated using an indirect method, based on the functional relationship between incidence (I) and mean duration (D), commonly expressed as P = I x D. Data on DMD birth prevalence have been collected in 12 European countries including articles published since 1983 until 2019 (see Table 1).

Table 1. Summary of literature review for the prevalence of DMD in EU countries

Author, Year of publication	**Country**	**Population**	**Study years**	**Birth prevalence/ 100.000 live male births**
Dellamonica, 1983	France	Blood samples of 158,000 newborns obtained 4 to 8 days postnatally	1978	16.9
Leth, 1985	Denmark	445 patients with progressive muscular dystrophy alive January 1st 1965	1965–1975	22.2
Scheuerbrandt, 1986	West Germany	-	1977–1984	27.2
Tangsrud, 1989	Southern Norway	All boys with a known history of Duchenne muscle dystrophy born during the period 1968– 1977	1968–1977	21.9
Van Essen, 1992	The Netherlands	All males with DMD both born and diagnosed in the period 1961–1982 in the Netherlands	1961–1982	23.7
Merlini, 1992	Italy	Children born between 1970 and 1989	1970–1982	25.8
Peterlin, 1997	Slovenia	DMD cases diagnosed in the period 1969–1984	1969–1984	13.8
Drousiotou, 1998	Cyprus	30,014 newborn males screened for DMD	1992–1997	16.7

Jeppesen, 2003	Denmark	Danish live born males from 1972 to 2001	1992–1996	18.8
Talkop, 2003	Estonia	All patients with DMD born and diagnosed in the period 1977– 1999 in Estonia	1986–1990	17.7
Eyskens, 2006	Belgium	281,214 newborn males screened for dystrophinopathy	1979–2003	18.2
Wahlgren, 2019	Sweden	All patients with DMD born and diagnosed in the period 1970–2019	1970–2019	13.8

The sponsor calculated a mean birth prevalence of 19.7, ranging from 13.8 (lowest rate by Peterlin et al., 1997 and Wahlgren et al., 2019) to 27.2 (highest by Scheuerbrandt et al., 1986) per 100.000 male births.

Figures on the live birth male population within Europe is not available for the last two years (2021/2022), therefore yearly birth rate was estimated from 2020. Taking into consideration the yearly birth rate of approximately 2.1 million male births in 2020 (Eurostat 2020), up to 414 cases of DMD per year in the EU are estimated in this way. If up to 414 DMD-affected male patients per year exist, dividing by the total male population for Europe which in 2022 was 218,344,994 (Eurostat 2022), yearly incidence rate is approximately 0.02/10,000 males in the EU and 0.01/10,000 total EU population (assuming a total EU population of 446.7Mio as per EUROSTAT 2022)

Broomfield et al reported a full overview of mortality across the lifetime of a patient with DMD, thus providing a representative estimate of life expectancy for this patient population. A systematic review of the published literature on mortality in DMD up to July 2020 was undertaken, specifically focusing on publications in which Kaplan-Meier (KM) survival curves with age as a timescale were presented (Broomfield et al., 2021). Of 1,177 articles identified, 14 publications met the inclusion criteria and provided data on 2,283 patients, of whom 1,049 had died. Median life expectancy was 22.0 years (95% confidence interval [CI] 21.2, 22.4) (Broomfield et al., 2021).

Based on the functional relationship (P = I x D) between incidence (I) and mean duration (D), if yearly incidence rate (0.01/10,000) is multiplied by the assumed duration of 22 years, an approximately **0.22** /10,000 prevalence is estimated.

The COMP accepted a prevalence estimate of 0.2 in 10,000 persons in the EU, in line with the sponsors proposal.

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

Ataluren (Translarna)

The only authorized product for the treatment of Duchenne muscular dystrophy in the EU is Ataluren (Translarna). The therapeutic indication of this product according to the 4.1 SmPC wording is as follows: *Translarna is indicated for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 2 years and older (see section*

5.1). The presence of a nonsense mutation in the dystrophin gene should be determined by genetic testing (see section 4.4).

The COMP does not consider Ataluren a satisfactory method for the purpose of this procedure as it is only a therapeutic option for a more restricted DMD patient population as compared to the one of Agamree. Only DMD patients which carry a nonsense mutation in the DMD gene which leads to a premature stop codon in the dystrophin mRNA are eligible for the treatment with Ataluren. This population consists of approximately 10–15% of boys with DMD (Muntoni et al., 2019). Agamree does not have this restriction. The sponsor further points out that patients treated with Ataluren still receive glucocorticoids over the course of their life to achieve best possible outcomes in terms of slowing their motor function decline and delaying loss of ambulation.

Therefore, the COMP does not consider Ataluren a satisfactory method for the purpose of this procedure as it only covers a more restricted DMD patient population as compared to the one of Agamree.

The COMP further notes that the CHMP has recommended not renewing the marketing authorisation for Translarna (ataluren) following their full re-evaluation of the benefits and risks of the medicine in September 2023 (https://www.ema.europa.eu/en/news/ema-recommends-non-renewal-authorisation-duchenne-muscular-dystrophy-medicine-translarna). The CHMP opinion is sent to the European Commission, which will issue a final legally binding decision applicable in all EU Member States. For the time being however, Ataluren is still considered authorized in the EU.

Glucocorticoids

Consensus treatment guidelines recommend the use of glucocorticoids (The Diagnosis and Management of Duchenne Muscular Dystrophy. Bushby K et al. Part 1: Lancet Neurol. 2010 Jan; 9(1):77-93 and Part 2: Lancet Neurol. 2010 Feb; 9(2):177-189). Glucocorticoids slow the decline in muscle strength and function in DMD. Their use has also been shown to reduce the risk of scoliosis and stabilise pulmonary function. Cardiac function might also improve, with limited data to date indicating a slower decline in echocardiographic measures of cardiac dysfunction. There are no generally accepted guidelines about the best time to initiate glucocorticoid therapy. However, the consensus treatment guideline by Bushby et al (2010) does not recommend initiation while the patient continues to still make progress in gaining motor skills (until approximately age 4–6 years in most DMD boys). The initiation of glucocorticoids is usually suggested by the physician once the plateau phase in motor skills has been clearly identified, usually at age 4–8 years. Starting steroids when in the full decline phase or when ambulation is more marginal is still recommended but might be of more limited benefit. In patients who have used glucocorticoids while ambulatory, many experts continue medication after loss of ambulation, with the goal of preserving upper limb strength, reducing progression of scoliosis, and delaying decline in respiratory and cardiac function.

While corticosteroids (primarily prednisone and deflazacort) are widely prescribed for the treatment of DMD, the COMP noted that this class of medicinal products is used off-label in the EU. This means that currently, no authorised glucocorticoids are formally indicated for the treatment of Duchenne muscular dystrophy, as none of the relevant Summaries of Product Characteristics (SmPC) include an indication for the treatment of DMD in the EU. Therefore, corticosteroids cannot be considered a satisfactory method for the treatment of DMD, for the purpose of this procedure. This position is based on Article 3(1)(b) of Regulation (EC) No 141/2000, which expressly links the notion of "satisfactory method of treatment" with the requirement of (prior) authorisation. This position is further supported by the 2016 "Commission Notice Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products", which states that:

"Any reference to an authorised medicinal product" must be limited to the terms of the marketing authorisation. Therefore, a product that is administered or applied outside the approved summary of product characteristics ('off-label' use) cannot be considered a satisfactory method for the purposes of Article 3(1)(b)".

The COMP further pointed out that in exceptional cases a satisfactory method may also include a medicinal product which is authorised for the treatment of "exactly the same set of symptoms" (Commission Notice 2016/C 424/03). This would be applicable in cases where the medicinal product in question would only address specific symptoms within a given therapeutic indication/condition and where there are authorised products which are indicated for the treatment of these particular symptoms. However, this exceptional case does not apply for Agamree vis a vis authorised corticosteroid, as Agamree is not indicated for the treatment of particular symptoms of DMD which would in turn be reflected in the SmPCs of corticosteroids. Agamree is in fact indicated to treat the condition as such, i.e. the approved therapeutic indication is "*AGAMREE is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients aged 4 years and older.*"

COMP conclusion

In view of the above, the COMP concludes that corticosteroids cannot be considered satisfactory methods for the treatment of DMD, for the purpose of this procedure. Nevertheless, from a clinical/public health point of view the COMP emphasized the importance of considering the safety and efficacy profile of Agamree in relation to the one of the routinely used standard of care therapy with corticosteroids. In this regard the COMP noted the sponsors pivotal clinical trial of Agamree which, in addition to a placebo-control arm, also included a prednisone-control arm. However, as corticosteroids are not a legally defined satisfactory method, the significant benefit of Agamree vis a vis corticosteroids was not assessed.

With regards to Translarna (ataluren), the COMP noted that Agamree (vamorolone) has proven efficacious in the treatment of Duchenne muscular dystrophy, not restricted to any patient subgroups. Therefore, Agamree represents a therapeutic option for a broader patient population, not covered by the therapeutic indication of Translarna. Consequently, Translarna is not considered a relevant satisfactory method in this orphan maintenance procedure.

Significant benefit

Not applicable due to the authorized medicinal product not being qualified as satisfactory methods.

4. COMP list of issues

Not applicable.

5. COMP position adopted on 13 October 2023

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 Duchenne muscular dystrophy (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 0.2 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to progressive muscle weakness eventually affecting all voluntary muscles; this is followed by dilated cardiomyopathy and cardiac output decrease, leading to terminal respiratory or cardiac failure;
- at present, no satisfactory method has been authorised in the European Union for the treatment of the entirety of patients covered by the therapeutic indication of Agamree.

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 Agamree, 17,21-dihydroxy-16-methyl-pregna-1,4,9(11)-triene-3,20-dione, vamorolone for treatment of Duchenne muscular dystrophy (EU/3/14/1309) is not removed from the Community Register of Orphan Medicinal Products.