15 September 2022
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Nulibry (cyclic pyranopterin monophosphate)
Treatment of molybdenum cofactor deficiency type A
EU/3/10/777

Sponsor: Comharsa Life Sciences Limited

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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1. Product and administrative information

Product	
Designated active substance(s)	Cyclic pyranopterin monophosphate
Other name(s)	-
International Non-Proprietary Name	Fosdenopterin
Tradename	Nulibry
Orphan condition	Treatment of molybdenum cofactor deficiency type A
Sponsor's details:	Comharsa Life Sciences Limited 10 Earlsfort Terrace Dublin 2 D02 T380 Co. Dublin Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Orphatec Pharmaceuticals GmbH
COMP opinion	2 June 2010
EC decision	20 September 2010
EC registration number	EU/3/10/777
Post-designation procedural history	
Change of sponsor name	Orphatec Pharmaceuticals GmbH changed name to Colbourne Pharmaceuticals GmbH – EC letter 22 January 2013
Transfer of sponsorship	Transfer from Colbourne Pharmaceuticals GmbH to Alexion Europe SAS – EC decision of 15 March 2013
Change of sponsor address	EC letter 20 February 2015
Transfer of sponsorship	Transfer from Alexion Europe SAS to Voisin Consulting – EC decision 18 January 2019
Transfer of sponsorship	Transfer from Voisin Consulting to Comharsa Life Sciences Limited – EC decision 6 May 2021
COMP opinion on review of orphan designation at the time of marketing authorisation	26 April 2022
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Johann Lodewijk Hillege/ Ewa Balkowiec Iskra
Applicant	Comharsa Life Sciences Limited
Application submission	4 November 2021
Procedure start	25 November 2021
Procedure number	EMA/H/C/005378
Invented name	Nulibry
Proposed therapeutic indication	Treatment of molybdenum cofactor deficiency type A Further information on Nulibry can be found in the European public assessment report (EPAR) on the Agency's website: ema.europa.eu/en/medicines/human/EPAR/nulibry
CHMP opinion	21 July 2022

COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Olimpia Neagu / Elisabeth Penninga
Sponsor's report submission	26 November 2021
COMP discussion	11-13 April 2022
COMP opinion (adoption via written procedure)	25 July 2022

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2010 was based on the following grounds:

Whereas, the Committee for Orphan Medicinal Products (COMP), having examined the application, concluded:

- for the purpose of orphan designation, the COMP considered that the indication should be renamed as "treatment of molybdenum cofactor deficiency type A";
- molybdenum cofactor deficiency type A (hereinafter referred to as "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;
- the condition is chronically debilitating and life threatening due to poor overall survival;
- there is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

The COMP recommends the designation of this medicinal product, containing cyclic pyranopterin monophosphate, as an orphan medicinal product for the orphan indication: treatment of molybdenum cofactor deficiency type A.

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 approved therapeutic indication "treatment of patients with molybdenum cofactor deficiency (MoCD) Type A" falls within the scope of the designated orphan condition "Treatment of molybdenum cofactor deficiency type A".

MoCD is an autosomal recessive inborn error of metabolism. MoCD Type A is the result of a change in a gene called MOCS1. This change prevents the body from producing cyclic pyranopterin monophosphate (cPMP), and ultimately molybdenum cofactor (MoCo). The lack of MoCo leads to high sulfite and S-sulfocysteine (SSC) levels. Two-thirds of MoCD patients have Type A, the remainder have type B and C, depending on the deficient gene.

Symptom onset in the classically described MoCD type A patient population is in utero or shortly after birth and thus represent the severely affected patient population. In recent years it has become clear that there are also milder/late-onset forms of MoCD with the age of onset generally after 6 months of age and with a very heterogeneous clinical picture. Patients usually present with treatment resistant seizures, severe brain damage and psychomotor retardation. Neurological decline is rapid and death usually occurs at the neonatal period or at early age for milder cases.

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

Molybdenum cofactor deficiency (MoCD) is a lethal autosomal recessive disease that causes a severe clinical picture with progressive encephalopathy due to the deficiency of molybdenum-dependent enzymes. Patients with MoCD usually present symptoms shortly after birth, such as intractable seizures, axial hypotonia, and limb hypertonia, metabolic acidosis, intracranial haemorrhage, exaggerated startle reactions, and failure to thrive. The seizures are usually tonic-clonic and difficult to control. Although milder cases with later onset and less severe symptoms have been identified, the prognosis is generally poor with death commonly occurring in the neonatal period due to severe and rapidly progressive neurological damage as a result of accumulation of toxic levels of sulphite in the body causing brain damage. Patients who survive the neonatal period usually develop encephalopathy and serious psychomotor retardation; many patients develop microcephaly and ocular abnormalities such as lens dislocation, spherophakia, iris coloboma, nystagmus, and enopthalmos. Cerebral blindness may occur.

Number of people affected or at risk

The sponsor's prevalence estimate is still within the range of the previously accepted value from 2010, at time of initial orphan designation which was less than 0.01 per 10,000 persons in the EU. The sponsor conducted a comprehensive updated literature review which includes references published between 2010 and September 2021. These references include single case reports as well as reviews and cohort study reports. Based on these data the sponsor concludes that the prevalence of MoCD Type A remains stable around 0.005 per 10,000 persons in the EU.

From 2010 to September 2021, only 5 case reports with 6 patients diagnosed with MoCD Type A have been identified in EU countries; they were reported in Germany and the Netherlands. These reports suggest 0.6 case per year in both countries. Assuming a total population of 100,602,371 inhabitants in both countries in 2020 (Eurostat) and a median survival for the MoCD Type A population of 36 months (Mechler et al., 2015), the calculated prevalence in 2019 from the publication of is 0.00018 per 10,000 inhabitants (0.00006*3).

With regards to the reviews and cohort study reports published between 2010 and September 2021 with patients diagnosed with MoCD Type A in EU countries 4 different references have been identified; they concern reports from Germany, Spain and the Netherlands.

Table 1. References (review, cohort study reports) reporting MoCD Type A patients in the EU population between 2010 and September 2021

First author	Country	Period (duration in years)	Number of MoCD Type A
(Belaidi et al., 2011)	Germany	Unknown	2
(Reiss and Hahnewald, 2011)	Germany	Through September 2010	40
(Schwahn et al., 2015)	Germany, Netherlands	Between June 2008 and January 2013 (4.5 years)	4
(Marin-Valencia et al., 2010)	Spain	January 2000 to December 2007 (7 years)	1

The calculated prevalence of MoCD Type A from case reports, reviews and cohort study reports is presented in Table 2 below.

Table 2. Prevalence for MoCD Type A from case reports, reviews and cohort study reports

Source/Publication	Case reports	(Reiss and Hahnewald, 2011)	(Schwahn et al., 2015)	(Marin-Valencia et al., 2010)
Calculated prevalence (per 10,000)	0.00018	0.005	0.0003	0.00009

In order to have a conservative approach, the highest prevalence calculated from the literature search will be extrapolated to the European Union. Therefore, the prevalence of MoCD Type A in the EU is estimated to be 0.005 per 10,000 inhabitants.

Therefore, the COMP concluded that the previously accepted prevalence estimate of less than 0.01 per 10,000 persons in the EU is still valid.

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

MoCD Type A is a serious and often fatal disease for which there are no approved medicinal products available in any European country. Apart from supportive care, there are no treatment options for patients with MoCD Type A. For management of seizures, various combinations of antiepileptic drugs are used.

Significant benefit

Not applicable.

4. COMP position adopted on 25 July 2022

The Committee for Orphan Medicinal Product (COMP) considered that the designated orphan condition is "treatment of molybdenum cofactor deficiency type A."

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 molybdenum cofactor deficiency type A (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be less than 0.01 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to progressive encephalopathy with treatment resistant seizures and life threatening due to poor overall survival;
- there is, at present, no satisfactory treatment that 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 Nulibry, cyclic pyranopterin monophosphate, fosdenopterin (as free base anhydrous) for treatment of molybdenum cofactor deficiency type A (EU/3/10/777) is not removed from the Community Register of Orphan Medicinal Products.