17 December 2020
EMADOC-1700519818-576428
Committee for Orphan Medicinal Products

# Orphan Maintenance Assessment Report

Libmeldy (Autologous CD34+ cells transfected with lentiviral vector containing the human arylsulfatase A cDNA)
Treatment of metachromatic leukodystrophy
EU/3/07/446
Sponsor: Orchard Therapeutics (Netherlands) B.V.

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

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|---|---|
| **Product** | |
| Designated active substance | Autologous CD34+ cells transfected with lentiviral vector containing the human arylsulfatase A cDNA |
| Other name | Autologous CD34+ cell enriched population that contains hematopoietic stem and progenitor cells transduced ex vivo using a lentiviral vector encoding the human arylsulfatase A gene |
| International Non-Proprietary Name | N/A |
| Tradename | Libmeldy |
| Orphan condition | Treatment of metachromatic leukodystrophy |
| Sponsor's details: | Orchard Therapeutics (Netherlands) B.V.<br>Prins Bernhardplein 200<br>1097 JB Amsterdam Noord-Holland<br>Netherlands |
| **Orphan medicinal product designation procedural history** | |
| Sponsor/applicant | Fondazione Telethon, Italy |
| COMP opinion | 8 March 2007 |
| EC decision | 13 April 2007 |
| EC registration number | EU/3/07/446 |
| **Post-designation procedural history** | |
| Transfer of sponsorship | Transfer from Fondazione Telethon to GlaxoSmithKline Trading Services Limited – EC decision of 30 July 2014 |
| Transfer of sponsorship | Transfer from GlaxoSmithKline Trading Services Limited to Orchard Therapeutics Ltd – EC decision of 31 July 2018 |
| Transfer of sponsorship | Transfer from Orchard Therapeutics Ltd to Orchard Therapeutics (Netherlands) B.V. – EC decision of 25 March 2019 |
| **Marketing authorisation** | |
| Rapporteur / Co-rapporteur | Carla Herberts / Paolo Gasparini |
| Applicant | Orchard Therapeutics (Netherlands) B.V. |
| Application submission | 8 November 2019 |
| Procedure start | 28 November 2019 |
| Procedure number | EMA/H/C/005321 |
| Invented name | Libmeldy |

| | |
|---|---|
| Proposed therapeutic indication | Libmeldy is indicated for the treatment of metachromatic leukodystrophy (MLD) characterized by biallelic mutations in the arysulfatase A (ARSA) gene leading to a reduction of the ARSA enzymatic activity:<br>-in children with late infantile or early juvenile forms, without clinical manifestations of the disease,<br>-in children with the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline<br><br>Further information on Libmeldy can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Libmeldy |
| CHMP opinion | 15 October 2020 |
| **COMP review of orphan medicinal product designation procedural history** | |
| COMP rapporteur(s) | Armando Magrelli / Elisabeth Johanne Rook |
| Sponsor's report submission | 08 January 2020 |
| COMP discussion and adoption of list of questions | 14-16 July 2020 |
| COMP opinion (adoption via written procedure) | 19 October 2020 |

## 2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2007 designation was based on the following grounds:

- for the purpose of orphan designation, the COMP considered that the active ingredient should be reworded as "autologous CD34+ cells transfected with lentiviral vector containing the human arylsulfatase A cDNA";
- metachromatic leukodystrophy (hereinafter referred to as "the condition") was estimated to be affecting less than 0.5 in 10,000 persons in the Community, at the time the application was made;
- the condition is chronically debilitating and life threatening in particular due to the development of progressive degenerative disease and short life expectancy;
- there is, at present, no satisfactory treatment that has been authorised in the Community for patients affected by the condition.

# 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**

Metachromatic leukodystrophy (also known as arylsulfatase A deficiency) is an autosomal recessively inherited disease characterized by deficient activity of the lysosomal enzyme arylsulfatase A. Its deficiency results in accumulation of sulfatides in neural and visceral tissues, and causes demyelination of the central and peripheral nervous system (Beerepoot, Orphanet J Rare Dis 2019 Nov 4;14(1):240). This leads to a broad range of neurological symptoms with three clinical subtypes: late-infantile, juvenile, and adult. There have not been any relevant changes in the classification and the condition since orphan designation and it is still a distinct medical entity valid for the purpose of the orphan framework.

The therapeutic indication:

*"Libmeldy is indicated for the treatment of metachromatic leukodystrophy (MLD) characterized by biallelic mutations in the arysulfatase A (ARSA) gene leading to a reduction of the ARSA enzymatic activity:*

*-in children with late infantile or early juvenile forms, without clinical manifestations of the disease*

*-in children with the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline"*

falls entirely within the scope of the designated orphan condition "Treatment of metachromatic leukodystrophy".

**Intention to diagnose, prevent or treat**

The medical plausibility is confirmed on the basis of a positive benefit/risk assessment of the CHMP. Please refer to the EPAR for more information:
https://www.ema.europa.eu/en/medicines/human/EPAR/Libmeldy

**Chronically debilitating and/or life-threatening nature**

The condition is chronically debilitating in particular due to peripheral and central demyelination resulting in abroad range of neurological symptoms including peripheral neuropathy, intellectual impairment, behavioural difficulties, motor function disturbances, ataxia, optic atrophy. The condition is also life-threatening with premature death, which can be within five years for the late infantile form.

**Number of people affected or at risk**

The sponsor conducted a literature review and identified data on the birth prevalence of MLD in Europe between 2007 and 2019. It is reported that the most recent prevalence data for MLD in the EU according to Orphanet, pertains to a prevalence of 0.1 to 0.9 per 100,000 (Orphanet 2019) and a birth prevalence of 1.47 (Orphanet report series, 2019).

Further relevant studies were also identified and used as follows: A yearly incidence rate was calculated by assuming a birth prevalence of 0.38 (lowest rate in reviewed literature reported by Lugowska et al 2011) to 1.73(highest by Hult et al 2014) per 100.000 births, and taking into consideration the yearly birth rate of approximately 4.96 million births in 2018 (Eurostat 2018). Up to 86 cases per year in the EU were estimated in this way.

The sponsor assumed that 40 to 60% of patients have the Late Infantile (LI) variant, 20 to 40% have the juvenile variant (early juvenile [EJ] + late juvenile [LJ]), and approximately 20% have an adult variant (Gieselmann, 2010; Gomez-Ospina, 2006;Heim, 1997; Ługowska, 2005; Poorthuis, 1999). Respective life expectancies were also assumed from literature (in particular Mahmood, J Child Neurol. 2010;25(5):572- 80) as per the table below:

**Table 1**, sourced from the sponsor's documents.

| Variant | % MLD population affected | Estimated life expectancy |
|---|---|---|
| Late Infantile | 50% | 10 years* |
| Juvenile | 30% | 25 years |
| Adult | 20% | 50 years |

*Maximum life expectancy estimated in this age group.

Based on these assumptions, it was purported that the life expectancy of any MLD patient may be approximated to 22.5 years (5 + 7.5 + 10 years). The EU life expectancy is currently approximately 81 years (Eurostat, 2020), therefore, on average, an MLD patient can be expected to have approximately 28% of a normal lifespan. The sponsor estimated that 1.1 cases (all MLD variants) per 100,000 live births are seen in the European Union. The prevalence, based on a life expectancy of 28% of a normal life span, is therefore considered by the sponsor as 28% of 0.11 per 10,000 i.e. 0.03 per 10,000.

The COMP considered that the above methodology does not follow the incidence x duration formula. However, if up to 86 patients per year exist (yearly incidence rate of approximately 0.002/10,000) and this were to be multiplied by the assumed duration of approximately 20 years, an approximately 0.04 /10,000 complete prevalence would be estimated.

It was therefore considered that an overall conclusion of less than 0.1 in 10 000 may be conservatively accepted, to also accommodate the paucity of epidemiological evidence at the time of review.

### 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**

No authorised product for metachromatic leukodystrophy have been identified.

**Significant benefit**

Not applicable.

# 4. COMP position adopted on 19 October 2020

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 metachromatic leukodystrophy (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 chronically debilitating in particular due to peripheral and central demyelination resulting in a broad range of neurological symptoms including peripheral neuropathy, intellectual impairment, behavioural difficulties, motor function disturbances, ataxia, optic atrophy. The condition is also life-threatening with premature death within five to ten years for the late infantile form;
- there is, at present, no satisfactory method of treatment 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 Libmeldy, autologous CD34+ cells transfected with lentiviral vector containing the human arylsulfatase A cDNA, for treatment of metachromatic leukodystrophy (EU/3/07/446) is not removed from the Community Register of Orphan Medicinal Products.