19 November 2020
EMA/OD/0000034914
EMADOC-1700519818-576401
Committee for Orphan Medicinal Products

# Orphan Maintenance Assessment Report

Oxlumo (lumasiran)
Treatment of primary hyperoxaluria
EU/3/16/1637
Sponsor: Alnylam 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

| **Product** | |
|---|---|
| Designated active substance | Synthetic double-stranded siRNA oligonucleotide directed against hydroxyacid oxidase 1 mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues |
| Other name | NA |
| International Non-Proprietary Name | Lumasiran |
| Tradename | Oxlumo |
| Orphan condition | Treatment of primary hyperoxaluria |
| Sponsor's details: | Alnylam Netherlands B.V.<br>Antonio Vivaldistraat 150<br>1083 HP Amsterdam<br>Noord-Holland<br>Netherlands |
| **Orphan medicinal product designation procedural history** | |
| Sponsor/applicant | Alnylam UK Limited |
| COMP opinion | 18 February 2016 |
| EC decision | 21 March 2016 |
| EC registration number | EU/3/16/1637 |
| **Post-designation procedural history** | |
| Transfer of sponsorship | Transfer from Alnylam UK Limited to Alnylam Netherlands B.V. – EC decision of 21 February 2019 |
| **Marketing authorisation procedural history** | |
| Rapporteur / Co-rapporteur | Martina Weise/ Fátima Ventura |
| Applicant | Alnylam Netherlands B.V. |
| Application submission | 31 March 2020 |
| Procedure start | 23 April 2020 |
| Procedure number | EMA/H/C/005040 |
| Invented name | Oxlumo |
| Therapeutic indication | Treatment of primary hyperoxaluria type 1 (PH1) in all age groups<br><br>Further information on Oxlumo can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/oxlumo |
| CHMP opinion | 15 October 2020 |
| **COMP review of orphan medicinal product designation procedural history** | |
| COMP rapporteur(s) | Dinah Duarte / Vallo Tillmann |
| Sponsor's report submission | 12 May 2020 |
| COMP discussion | 8-10 September 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 2016 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing synthetic double-stranded siRNA oligonucleotide directed against hydroxyacid oxidase 1 mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues was considered justified based on results from valid preclinical in vivo disease models showing that the product can reduce deregulated urinary oxalate levels;
- the condition is life-threatening and chronically debilitating due to recurrent nephrolithiasis and progressive nephrocalcinosis leading to renal damage. The majority of the patients develop end stage renal disease during the 3rd to 5th decade of life;
- the condition was estimated to be affecting approximately 0.05 in 10,000 persons in the European Union, at the time the application was made;
- 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.

# 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 Primary Hyperoxaluria Type 1 (PH1) in all age groups" falls within the scope of the designated orphan condition "Treatment of primary hyperoxaluria".

Primary hyperoxaluria (PH) is an ultra-rare, progressive, serious and life-threatening, autosomal recessive inborn error of metabolism, resulting in increased endogenous hepatic production of oxalate, the key toxic metabolite responsible for the clinical manifestations of the disease. In addition to PH1, two other types of primary hyperoxaluria have been identified that result from different enzymatic defects; PH1 accounts for approximately 80% of PH cases and is the most clinically severe (Hoppe 2012).

**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**

There have been no changes to the life-threatening and chronically debilitating nature of the condition since the granting of the orphan drug designation in 2016 and there have been no newly approved therapies since that time.

PH1 can affect patients of all ages, but the serious and life-threatening aspects of the disease, including end stage renal disease (ESRD) and systemic oxalosis, often affect children under 18 years of age despite current standard of care. Approximately one quarter of all PH1 cases present as a severe infantile form of the disease, which is associated with a 5-fold higher risk of death compared to older patients with PH1 (Harambat, Fargue et al. 2010). Approximately one-third of PH1 patients experience recurrent kidney stones during childhood or early adulthood that require urologic procedures and hospitalizations that can have a serious impact on quality of life.

The condition remains chronically debilitating and life threatening.

**Number of people affected or at risk**

The sponsor performed a new calculation of prevalence of PH. The prevalence and sources of information collected for the frequency of Primary Hyperoxaluria included: Orphanet, 2013, van der Hoeven et al, 2012, van Woerden et al, 2003, Cochat et. al, 1995, Hoppe et al, 2005, Cochat et. al, 1995, Kopp and Leumann 1995, van Woerden et al, 2003, Cochat et. al, 1995, Kopp and Leumann 1995, Harambat et al, 2010 and Milliner, 2005.

In summary, the prevalence of PH and PH1 remain unchanged since the orphan designation was granted in 2016**.** Based on published literature, it is estimated that in the European Union PH affects a maximum of 0.05 in 10,000 people and PH1 affects a maximum of 0.04 in 10,000 people. This estimate is acceptable given the paucity of data and lack of indication that the prevalence changed.

## 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**

Currently, there are no approved therapies for PH. As PH is a heterogeneous disease, management is guided by the stage of disease and associated complications. The goals of treatment in PH are to reduce levels of urinary and plasma oxalate, which directly cause the renal and extra-renal manifestations of this disease, respectively. The European Hyperoxaluria Consortium (OxalEurope) was established in 2008 to bring together European clinicians and scientists with the intent to provide diagnostic and therapeutic recommendations for patients with PH (Cochat, Hulton et al. 2012). Some standard approaches for disease management include hyperhydration and inhibitors of crystallization, use of pyridoxine, use of dialysis and eventually kidney transplantation.

**Significant benefit**

Significant benefit is not applicable in this case.

# 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 primary hyperoxaluria (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.05 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 recurrent nephrolithiasis and progressive nephrocalcinosis leading to renal damage. Majority of the patients develop end stage renal disease during the 3rd to 5th decade of life;
- there is, at present, no satisfactory method for the 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 Oxlumo, synthetic double-stranded siRNA oligonucleotide directed against hydroxyacid oxidase 1 mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues, lumasiran, for treatment of primary hyperoxaluria (EU/3/16/1637) is not removed from the Community Register of Orphan Medicinal Products.