Risk Management Plan (RMP) Summary

for

Oxlumo® (Lumasiran)

Oxlumo, 94.5 mg / 0.5 mL, Injektionslösung
Zl-Nr. 68239

Alnylam Switzerland GmbH

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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Oxlumo is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Oxlumo in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Alnylam Switzerland GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Oxlumo.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ESRD	End-stage renal disease
NCI ODWG	National Cancer Institute Organ Dysfunction Working Group
PASS	Post-authorisation safety study
PH1	Primary hyperoxaluria type 1
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Queries
TBILI	Total bilirubin
ULN	Upper limit of normal

SUMMARY OF THE RISK MANAGEMENT PLAN FOR OXLUMO

This is a summary of the risk management plan (RMP) for Oxlumo. The RMP details important risks of Oxlumo, how these risks can be minimized, and how more information will be obtained about Oxlumo's risks and uncertainties (missing information).

Oxlumo's Information for Health Care Professionals and its Information for Patients give essential information to healthcare professionals and patients on how Oxlumo should be used. They can be found at www.swissmedicinfo.ch.

This summary of the RMP for Oxlumo should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which are part of the European Public Assessment Report (EPAR).

Important new safety concerns or changes to the current ones will be included in updates of Oxlumo's RMP.

I. The medicine and what it is used for

Oxlumo is authorized for the treatment of primary hyperoxaluria type 1 (PH1) in all age groups. It contains lumasiran as the active substance and it is administered by subcutaneous injection.

Further information about the evaluation of Oxlumo's benefits can be found in Oxlumo's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Oxlumo, together with measures to minimize such risks and the proposed studies for learning more about Oxlumo's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the Package Leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and analyzed regularly, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

There are no *additional risk minimization* measures for Oxlumo in Switzerland at this time.

If important information that may affect the safe use of Oxlumo is not yet available, it is listed under 'missing information'.

II.A List of important risks and missing information

Important risks of Oxlumo are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of the drug. There are no important identified risks for Oxlumo. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the longer-term use of the medicine);

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	• Hepatic effects
Missing information	• Longer-term safety (>1 year) • Use in patients with hepatic impairment • Use in patients with severe renal impairment or ESRD, including patients on dialysis • Use in pregnant or lactating women and effects on pregnancy outcomes • Use in patients <2 years of age • Immunogenicity

Abbreviation: ESRD=end-stage renal disease.

II.B Summary of important risks and Missing Information

Important Potential Risk: Hepatic Effects	
Evidence for linking the risk to the medicine	Lumasiran is directed for delivery to the liver. A potential mechanism by which lumasiran could cause hepatic effects is not known. In nonclinical (animal) studies, minor and reversible changes were observed. The relevance of these nonclinical findings to humans remains unclear. No clinically significant liver events or abnormal liver function tests indicative of hepatotoxicity (liver toxicity) have been observed, however, given the relatively small size of the safety database, potential effect of lumasiran on the liver has not been characterized. Therefore, hepatic effects are included as an important potential risk to ensure further characterization of this potential safety concern.
Risk factors and risk groups	Unknown.

Risk minimization measures	Routine risk communication: • Not applicable Routine risk minimization activities recommending specific clinical measures to address the risk: • Not applicable Other routine risk minimization measures beyond the Product Information: Legal status: Prescription-only medication
Additional pharmacovigilance activities	Hepatic effects will be monitored and further characterized in the ongoing clinical studies Study ALN-GO1-002, Study ALN-GO1-003, Study ALN-GO1-004 and Study ALN-GO1-005, and the ALN-GO1-007 Observational PASS

Missing Information: Longer-term safety (>1 year)	
Risk minimization measures	Routine risk communication: A summary of the safety profile of lumasiran in the clinical development program is provided in the Undesirable effects section (Section 4.8) of the SmPC.
Additional pharmacovigilance activities	Long-term safety will be evaluated as part of the ongoing studies Study ALN-GO1-002, Study ALN-GO1-003, Study ALN-GO1-004 and Study ALN-GO1-005, and the ALN-GO1-007 Observational PASS

Missing Information: Use in patients with hepatic impairment	
Risk minimization measures	Routine risk communication: • Information on the absence of data in patients with hepatic impairment is included in the Posology and method of administration section (Section 4.2) and Pharmacokinetic properties section (Section 5.2) of the SmPC. • Information that caution is required when treating patients with moderate or severe hepatic impairment is included in the Posology and method of administration section (Section 4.2) of the SmPC. • In the Warnings and Precautions section (Section 4.4) of the SmPC it is also included that patients with moderate or severe hepatic impairment should be monitored for potential decreased efficacy.
Additional pharmacovigilance activities	Use in patients with moderate or severe hepatic impairment will be evaluated as part of the ALN-GO1-007 Observational PASS

Missing Information: Use in patients with severe renal impairment or ESRD, including patients on dialysis	
Risk minimization measures	Routine risk communication: • Information on the limited data in patients with severe renal impairment, ESRD or patients on dialysis is included in the Posology and method of administration section (Section 4.2) and Pharmacokinetic properties section (Section 5.2) of the SmPC. • The following information is also included in the Warnings and Precautions section (Section 4.4) of the SmPC: Treatment with lumasiran increases plasma glycolate levels, which may increase the risk of metabolic acidosis or worsening of pre-existing metabolic acidosis in patients with severe or end-stage renal disease. These patients should therefore be monitored for signs and symptoms of metabolic acidosis.
Additional pharmacovigilance activities	Use in patients with severe renal impairment or ESRD, including patients on dialysis will be evaluated as part of the Study ALN-GO1-005 and ALN-GO1-007 Observational PASS

Missing Information: Use in pregnant or lactating women and effects on pregnancy outcomes	
Risk minimization measures	<u>Routine risk communication:</u> • Information on the lack of clinical data in pregnant women and in lactating women is included in the Fertility, pregnancy and lactation section (Section 4.6) of the SmPC, with a cross-reference to nonclinical data on embryo-fetal development, lactation, and fertility in the Preclinical safety data section (Section 5.3) of the SmPC. <u>Routine risk minimization activities recommending specific clinical measures to address the risk:</u> • Advice is provided to evaluate the benefits and risks of treatment with lumasiran during pregnancy and breastfeeding for the mother and infant, and the mother's clinical need for lumasiran in the Fertility, pregnancy, and lactation section (Section 4.6) of the SmPC and Section 2 of the Package Leaflet.
Additional pharmacovigilance activities	Use in pregnant or lactating women and effects on pregnancy outcomes will be evaluated as part of the ALN-GO1-007 Observational PASS

Missing Information: Use in patients <2 years of age	
Risk minimization measures	<u>Routine risk communication:</u> • Information on safety profile in pediatric population is provided in Section 4.8 and Section 5.2 of the SmPC. Information on limited data in children younger than 1 year of age is included in the Posology section (Section 4.2) and the Pharmacokinetic properties section (Section 5.2) of the SmPC. <u>Routine risk minimization activities recommending specific clinical measures to address the risk:</u> None
Additional pharmacovigilance activities	Use in patients <2 years of age will be evaluated as part of the Studies ALN-GO1-004, ALN-GO1-005, and ALN-GO1-007 Observational PASS.

Missing Information: Immunogenicity	
Risk minimization measures	Routine risk communication: • Information on immunogenicity is provided in Section 4.8 of SmPC. Routine risk minimization activities recommending specific clinical measures to address the risk: None
Additional pharmacovigilance activities	Immunogenicity will be evaluated as part of the ongoing studies: Study ALN-GO1-002, Study ALN-GO1-003, Study ALN-GO1-004 and Study ALN-GO1-005, and the ALN-GO1-007 Observational PASS.

Routine risk minimization activities as described in Section II B. are sufficient to manage the safety concerns of the medicinal product. No additional risk minimization measures are proposed.

II.C Post-authorization Development Plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization in Switzerland or specific obligations of Oxlumo.

II.C.2 Other studies in post-authorization development plan

Additional PV activities include monitoring of safety in the ongoing studies: Study ALN-GO1-002, Study ALN-GO1-003, Study ALN-GO1-004, and Study ALN-GO1-005, in addition to a planned prospective observational study.

- Study ALN-GO1-002:

  Study ALN-GO1-002 is an ongoing Phase 2 OLE study to evaluate the long-term safety, PK, and PD of lumasiran in adult and pediatric (≥6 years of age) patients with PH1 who completed Study 001B. Patients will receive lumasiran for up to 54 months.

- Study ALN-GO1-003:

  Study ALN-GO1-003 is an ongoing Phase 3, randomized, double-blind, placebo-controlled study with extension period designed to evaluate the efficacy and safety of lumasiran in adults and pediatric (≥6 years of age) patients with PH1. The 6-month double-blind period of the study was completed 06 November 2019. In the ongoing extension period, patients receive lumasiran for up to 54 months.

- Study ALN-GO1-004:

  Study 004 is an ongoing Phase 3 single-arm study in infants and children with PH1 aged ≥1 day to <6 years. Patients will receive a weight-based loading doses followed by a maintenance dose for up to 60 months.

- Study ALN-GO1-005:

  Study ALN-GO1-005 is an ongoing Phase 3 single-arm study to evaluate lumasiran in adult and pediatric patients of all ages with PH1 who have advanced disease with or without hemodialysis. Patients will receive a weight-based loading dose followed by a maintenance dose for up to 60 months.

- ALN-GO1-007: Observational Post Authorization Safety Study (PASS)

  The Sponsor plans to conduct a prospective observational longitudinal study (ALN-GO1-007), to characterize the longer-term safety and effectiveness of lumasiran in a real-world cohort of PH1 patients of all ages. The study will also collect and evaluate information on pregnancy complications, birth outcomes, breast feeding and infant outcomes in women exposed to lumasiran during pregnancy