CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214103Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214103
PDUFA Goal Date	December 3, 2020
OSE RCM #	2020-74
Reviewer Name	Mona Patel, PharmD, RAC
Team Leader	Laura Zendel, PharmD
Deputy Director	Cynthia LaCivita, PharmD
Review Completion Date	November 23, 2020
Subject	Evaluation of Need for a REMS
Established Name	lumasiran
Trade Name	Oxlumo
Name of Applicant	Alynylam Pharmaceuticals, Inc.
Therapeutic Class	HAO1-directed siRNA
Formulation	Subcutaneous Injection
Dosing Regimen	

Body Weight	Loading Dose	Maintenance Dose (begin 1 month after the last loading dose)
less than 10 kg	6 mg/kg once monthly for 3 doses	3 mg/kg once monthly
10 kg to less than 20 kg	6 mg/kg once monthly for 3 doses	6 mg/kg once every 3 months (quarterly)
20 kg and above	3 mg/kg once monthly for 3 doses	3 mg/kg once every 3 months (quarterly)

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Executive Summary

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for Oxlumo (lumasiran) for injection is necessary to ensure the benefits outweigh its risks. Alnylam Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 214103 for lumasiran with the proposed indication for the treatment of primary hyperoxaluria type 1 (PH1) in pediatric and adult patients. The risk associated with the use of Oxlumo includes injection site reactions. During the review of the application the indication was revised to the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary oxlate levels in pediatric and adult patients. The applicant did not submit a proposed REMS but did submit a risk management plan (RMP) for the European Union with this application. The RMP details risks of lumasiran, how the risks can be minimized, and how more information will be obtained about lumasiran's risks and uncertainities.

The Division of Risk Management (DRM) has determined that a REMS is not needed to ensure the benefits of lumasiran outweigh its risks. Lumasiran has proven to treat PH1 by lowering urinary oxlate levels in pediatric and adult patients, labeling was modified to reflect. Based on the clinical trials, the benefit-risk profile is acceptable and risk mitigation beyond labeling is not required. In general, hepatologists and nephrologists should be familiar with the risk of injection site reactions (ISRs) (i.e., redness, itching, pain, etc.,) that are associated with lumasiran as ISRs are a common risk of injectable drug products.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for Oxlumo (lumasiran) is necessary to ensure the benefits outweigh its risks. Alnylam Pharmaceuticals, Inc submitted a New Drug Application (NDA) 214103 for lumasiran with the proposed indication for the treatment of primary hyperoxaluria type 1 (PH1) in pediatric and adult patients. This application is under review in the Division of Cardiology and Nephrology (DCN). The applicant did not submit a proposed REMS but did submit a risk management plan for the European Union with this application.

2 Background

2.1 PRODUCT INFORMATION

Lumasiran, a new molecular entity[a], is a hydroxyacid oxidase 1 (HAO1)-directed small interfering ribonucleic acid (siRNA) which prevents synthesis of hepatic glycolate oxidase resulting in decrease oxalate production. Lumasiran is indicated for the treatment of primary hyperoxaluria type 1 (PH1) in pediatric and adult patients. During the review of the application the indication was revised to the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary oxlate levels in pediatric and adult patients.[1]

[a] FDAAA factor (F): whether the drug is a new molecular entity

Lumasiran is proposed to be available as a 189 mg/mL solution to be administered via subcutaneous injection by a healthcare professional in patients on a weight-based dosing regimen. For a typical adult dose, a loading dose is administered once monthly at 3 mg/kg once monthly for 3 doses and then a subsequent maintenance dose of 3mg/kg once every 3 months is administered on a quarterly basis (b) (4) for chronic use.[b] Lumasiran is granted orphan designation on February 8, 2016, and breakthrough therapy designation on February 23, 2018. Lumasiran has not been approved or marketed in any country.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 214103 relevant to this review:

- 2/8/2016: Orphan drug designation granted for lumasiran to treat primary hyperoxaluria type 1 (PH1) in pediatric and adult patients.
- 2/23/2018: Breakthrough therapy designation granted for lumasiran to treat PH1 in pediatric and adult patients.
- 4/26/2018: End of Phase 2 meeting held during which FDA noted willingness to accept a substantial change in urinary oxalate in patients with high baseline values as a basis for full approval of lumasiran for treatment of PH1
- 12/10/2019: Rolling review granted
- 12/20/2019: Rare pediatric disease designation granted for PH1
- 01/10/2020: Part 1 of 2 of rolling New Drug Application 214103 for lumasiran to treat PH1 received consisting of the nonclinical section of the NDA
- 2/24/2020: Pre-NDA meeting held during which applicant was advised to include a risk management plan with the NDA submission
- 4/3/2020: Part 2 of 2 of rolling New Drug Application 214103 for lumasiran to treat PH1 received consisting of the clinical and chemistry, manufacturing, and control sections of the NDA
- 4/24/2020: FDA sent information request (IR) to Alynylam for QT Evaluation Report Submission Checklist
- 4/28/20: FDA sent information request (IR) to Alynylam for additional statistical and efficacy data
- 5/1/2020: FDA received an amendment containing a response to 4/24/20 IR
- 5/4/2020: FDA received an amendment containing a response to 4/28/20 IR
- 6/23/20: FDA received an amendment containing additional data and datasets from Study 004 in PH1 patients <6 years of age.

[b] FDAAA factor (D): The expected or actual duration of treatment with the drug

- 6/30/20: FDA sent information request (IR) to Alynylam to provide additional clinical pharmacology information on safety, efficacy and dosing recommendation for Oxlumo
- 7/3/20: FDA received an amendment containing a response to 6/30/20 IR.
- 7/23/20: Sponsor Mid-Cycle Meeting
- 8/26/20: FDA sent information request (IR) to Alynylam with regards to the number of enrolled patients requiring dialysis.
- 8/27/20: FDA received a response via email to 8/26/20 IR and confirmed that none of the patients enrolled in Study 004 progressed to requiring dialysis
- 9/1/20: FDA sent an IR to Alynylam pertaining to Safety Update Report #1.
- 10/16/20: FDA sent clinical information request (IR) to Alynylam regarding meeting eligibility criteria for screen failures in Study 003
- 10/19/20: FDA received a response via email to 10/16/20 IR
- 10/22/20: FDA sent an IR to Alynylam regarding the number of patients with injection site reactions.
- 10/23/20:FDA received a response via email to 10/22/20 IR
    - FDA sent an IR to Alynylam requesting information on episodes of hypersensitivity reactions in Study 003
- 10/26/20: FDA received a response to 10/23/20 IR

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Primary hyperoxaluria type 1 (PH1) is a disease stemming from excessive hepatic oxalate production, caused by a deficiency of the liver peroxisomal enzyme alanine-glyoxylate aminotransferase (AGT). PH1 accounts for approximately 80% of primary hyperoxaluria cases and is the most clinically severe. Oxalate is excreted by the kidneys, as a result, patients with PH1 have an increased concentration of oxalate in the urine, with consequent deposition of insoluble calcium oxalate crystals in the kidney and urinary tract. The crystal deposition and associated inflammation causes progressive damage, leading to renal impairment and end-stage renal disease (ESRD). As renal function declines due to disease progression, oxalate levels increase in plasma. Consequently, calcium oxalate crystals deposit in extrarenal tissues, causing systemic oxalosis, which affects the bone, retina, heart, and skin. Patients with advanced PH1 experience significant comorbidities associated with ESRD, systemic oxalosis, and eventually death. In the absence of effective treatment, disease progression can be rapid and death from ESRD and/or complications from oxalosis inevitable.[c, 2] The incidence of PH1 is approximately 1 in 120,000 live births,

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

and the prevalence is 1 to 3 per million in North America and Europe.[c, 3] More than half of PH1 patients develop symptoms before 6 years of age, and 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.[4] Also, approximately one-third of PH1 patients experience recurrent kidney stones during adolescence or early adulthood that require urologic procedures and hospitalizations that can have a serious impact on quality of life.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

There are no FDA-approved therapies for the treatment of PH1. However, therapies such as hyperhydration, crystallization inhibitors, pyridoxine, and hemo- and peritoneal dialysis are all employed to reduce levels of urinary and/or plasma oxalate. In patients with preserved renal function, hyperhydration and crystallization inhibitors are used in an attempt to slow the progression of disease and decrease renal stones. Pyridoxine (vitamin B6) is used in patients with certain genetic mutations to stabilize alanine:glyoxylate aminotransferase and correct the enzymatic defect. However, it is effective in only 5% of patients. In patients with advanced disease who can no longer renally offload excess oxalate, intensive hemodialysis (6 days per week) with supplemental peritoneal dialysis is administered. These therapies are limited in their effectiveness, and despite their use, disease manifestations of PH1 still progress in the majority of patients. Given that the enzymatic deficiency in PH1 is in the liver, the only metabolic cure for PH1 is liver or liver-kidney transplantation; however, transplantation is associated with significant morbidity and mortality.

4 Benefit Assessment

The efficacy and safety of lumasiran to treat primary hyperoxaluria type 1 (PH1) in pediatric and adult patients was derived primarily from two Phase 3 studies [Study 003 (Illuminate-A) and Study 004 (Illuminate-B)] comparing lumasiran versus placebo twice daily. Supportive efficacy data was also derived from the Phase 1/2 Study 001B and ongoing Phase 2 OLE Study 002.

Study 003 is a randomized (2:1), double-blind (DB), placebo-controlled multinational, Phase 3 study designed to evaluate the efficacy and safety of lumasiran in adults and children ≥6 years old with PH1. The study includes a 6-month, placebo-controlled, DB period followed by an extension period (ongoing) in which patients originally assigned to lumasiran continued on lumasiran, and patients originally assigned to placebo switched to lumasiran. In the DB period, patients were randomized (2:1) to dosing with 3 mg/kg lumasiran or placebo, with dosing every month for 3 months followed by dosing every 3 months. Patients were to continue their current standard of care regimen, including hyperhydration, crystallization inhibitors, and pyridoxine therapy, for the first 12 months of the study. The primary endpoint was percent change in 24 hours urinary oxalate (UOx) corrected for body surface area (BSA) from baseline to month 6. The primary analysis of the change in UOx used a restricted maximum likelihood (REML) based mixed-effect model repeated measures (MMRM) approach and sensitivity analyses were conducted and tested at a 2-sided level of significance ($p<0.05$). Key secondary efficacy endpoints measured the proportion of patients with 24-hour urinary oxalate levels ≤ULN and ≤1.5 x ULN and also percent reduction in plasma oxalate from baseline.

Thirty-nine subjects were enrolled. Twenty-six subjects received lumasiran and 13 patients received placebo during the 6-month DB period of whom 38 completed the DB period and 37 patients subsequently entered the extension period during which all patients are treated with lumasiran. The mean baseline 24-hour urinary oxalate excretion corrected for BSA was 1.84 with a standard error of the mean (SEM) of 0.62. The primary comparison is the LS mean treatment difference in percent change from baseline. The percent change from baseline to month 6 (average of months 3-6) was a LS mean difference of -53.5 (SEM 4.32 and p-value 1.685E-14) with lumasiran versus placebo which demonstrated a clinically meaningful and statistically significant effect.[5] Based on the clinical reviewer, clinical significance was achieved for the secondary endpoints of proportion of patients with 24-hour urinary oxalate levels ≤ULN (LS mean difference is 0.5 with a p-value=0.001) and ≤1.5 x ULN (LS mean difference is 0.8 with a p-value<0.0001). Statistical significance was achieved for the percent reduction in plasma oxalate (Pox) from baseline to month 6 (LS mean difference is 39.5 with a p-value<0.0001).[6,7]

Study 004 is an ongoing, multinational, Phase 3, single-arm study to evaluate the efficacy, safety, pharmacokinetics (PK), and pharmacodynamics (PD) of lumasiran in infants and children <6 years old with PH1.

The study open label includes a 6-month primary analysis period followed by a long-term extension period of up to 54 months, with patients receiving lumasiran using weight-based dosing. Patients <10 kg receive 6 mg/kg monthly for 3 months followed by 3 mg/kg monthly, patients ≥10 kg to <20 kg receive 6 mg/kg monthly for 3 months followed by 6 mg/kg every 3 months, and patients ≥20 kg receive 3 mg/kg monthly for 3 months followed by 3 mg/kg every 3 months. Patients were to continue their current standard of care regimen, including hyperhydration, crystallization inhibitors, and pyridoxine therapy, at least until the month 6 visit. The primary endpoint was percent change of spot urine oxalate to creatinine ratio from baseline to month 6. Key secondary efficacy endpoints measured the effect on absolute change spot UOx to creatinine ratio from baseline, change (percent and absolute) in POx from baseline, proportion of patients with UOx ≤ ULN and ≤ 1.5 xULN, and change from baseline in eGFR.

As of the data cut-off, sixteen subjects were enrolled and are being treated with lumasiran. None have reached month 6. A primary interim analysis is planned when the first 16 enrolled patients complete month 6 assessments or discontinue treatment. However, descriptive statistics show clinically meaningful reductions from baseline in urinary and plasma oxalate for patients treated with lumasiran during the first 3 months of Study 004. The mean baseline spot urine oxalate to creatinine ratio was 0.61 with a standard deviation (SD) of 0.42. The mean percent change from baseline to month 3 was 76.02 (SD=14.703). Based on the clinical reviewer, clinically meaningful reductions were also achieved during the first 6 months for the secondary endpoints of absolute change in spot UOx: creatinine ratio from baseline (mean percent change of -48% and SD=14.703) and change (percent and absolute) in POx from baseline (mean percent change of -46% and SD=26.42 and mean percent change of -8.27 and SD=8.83 respectively). As of the data cutoff, the proportion of patients with UOx≤ULN and≤1.5xULN had not been described in the application and eGFR remained stable in patients.

5 Risk Assessment & Safe-Use Conditions

The safety assessment of lumasiran was primarily based on patients from two ongoing, Phase 3 studies (Study 003 and Study 004) and supportive data from Studies 001B and 002. The studies included a total of 54 pediatric patients and 21 adult patients with PH1.

In the overall pooled safety dataset, 77.3% of patients in the lumasiran group had at least 1 AE. Adverse events reported in ≥5% of patients treated with lumasiran included injection site reactions (ISRs)(18.7%), headache (8.0%), and oropharyngeal pain, pyrexia, nasopharyngitis and injection site erythema (6.7%), along with gastroenteritis, rhinitis, injection site pain, and vomiting (5.3%).[8] Of these, ISRs were the focus of the safety review. For ISRs, 19 (25.3%) patients in the lumasiran group reported at least 1 ISR which included erythema (13.3%), pain (5.3%), pruritis (4%), and discomfort (2.7%).[9] No ISRs were serious or severe and none led to study drug discontinuation or withdrawal from the study. There were three (4%) patients treated with lumasiran that had adverse events mapping to the drug-related hepatic disorders standardized medra query. All 3 events were mild in severity and did not result in change to dose or withdrawal from the study. Based on clinical reviewer, injection site reactions can be managed with labeling and no additional risk minimization measures are considered necessary.

6 Expected Postmarket Use

The likely prescribers will be hepatologists and nephrologists in outpatient or inpatient settings. These prescrbers should be familiar with how to manage the injection site reactions that are associated with lumasiran as ISRs are a common risk of injectable drug products.

7 Risk Management Activities Proposed by the Applicant

The Applicant does not propose any risk management activities for lumasiran beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of Oxlumo on the basis of the efficacy and safety information currently available.

Primary hyperoxaluria type 1 (PH1) leads to deposition of insoluble calcium oxalate crystals in the kidney and urinary tract which can lead to renal impairment and end-stage renal disease (ESRD). Patients with advanced PH1 experience significant comorbidities associated with ESRD, systemic oxalosis, and eventually death. There are no FDA-approved therapies for the treatment of PH1. However, therapies such as hyperhydration, crystallization inhibitors, pyridoxine, and hemo- and peritoneal dialysis are all employed to reduce levels of urinary and/or plasma oxalate.

Two ongoing trials demonstrate effectiveness of lumasiran to be administered via subcutaneous injection for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary oxalate levels in pediatric and adult patients. Study 003 which evaluated patients on lumasiran compared to placebo showed clinical and statistical significance and clinically meaningful reductions from baseline in urinary

and plasma oxalate for infants and children < 6 years of age who are treated with lumasiran during the first 6 months of Study 004.

In the clinical development program thus far, no serious adverse events were identified in patients treated with lumasiran. The adverse events of interest are injection site reactions, none of which were serious or severe or led to study drug discontinuation or withdrawal from study. Overall, injection site reactions can be managed with labeling and no additional risk minimization measures are considered necessary.

Therefore, based on the data available and prescribing community's likely familiarity with the risk of injection site reactions that are associated with lumasiran due to ISR's being a common risk of injectable drug products, DRM is not recommending a REMS for lumasiran at this time.

9 Conclusion & Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits outweigh the risks. The safety concerns associated with lumasiran will be addressed in labeling, and in general, hepatologists and nephrologists who prescribe lumasiran should be familiar with the risk of injection site reactions that are associated with lumasiran and should be able to manage these risks. Should DCN have any concerns or questions or if new safety information becomes available, please send a consult to the Division of Risk Management.

10 Appendices

10.1 REFERENCES

[1] Alynylam Pharmaceuticals, Inc. US Prescribing Information for Oxlumo (lumasiran) (October 29, 2020)

[2] Alynylam Pharmaceuticals, Inc. Clinical Overview for Oxlumo (lumasiran), April 3, 2020

[3] Hopp K, Cogal AG, Bergstralh EJ, Seide BM, Olson JB, Meek AM, et al. Phenotype-Genotype Correlations and Estimated Carrier Frequencies of Primary Hyperoxaluria. J Am Soc Nephrol. 2015 Oct;26(10):2559-70.

[4] Harambat J, Fargue S, Acquaviva C, Gagnadoux MF, Janssen F, Liutkus A, et al. Genotype-phenotype correlation in primary hyperoxaluria type 1: the p.Gly170Arg AGXT mutation is associated with a better outcome. Kidney Int. 2010 Mar;77(5):443-9.

[5] Alynylam Pharmaceuticals, Inc. Summary of Clinical Efficacy for Oxlumo (lumasiran), April 3, 2020

[6] Mistry, Kirtida. Clinical Review for Oxlumo (lumasiran), NDA 214103, October 29, 2020

[7] Midcycle Meeting Presentation Oxlumo (lumasiran), NDA 214103, July 7, 2020

[8] Alynylam Pharmaceuticals, Inc. Summary of Clinical Safety for Oxlumo (lumasiran), April 3, 2020

[9] Benefit & Risk Scoping Meeting Presentation Oxlumo (lumasiran), NDA 214103, April 22, 2020

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