CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214103Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 214103: OXLUMO (Lumasiran) Injection

Integrated Quality Review

Recommendation: Approval

Drug Name	OXLUMO (Lumasiran) Injection
Dosage Form; Type of Product	Parenteral (Injection)
Indication	Indicated for the treatment of primary hyperoxaluria Type 1 (PH1) in pediatric and adult patients
Strength	189 mg/mL lumasiran (equivalent to 200 mg/mL lumasiran sodium) or 94.5 mg lumasiran (equivalent to 100 mg/mL lumasiran sodium) in 0.5mL
Route of Administration	For subcutaneous use
Rx/OTC Dispensed	Rx
Applicant	Alnylam Pharmaceuticals, Inc.
Submissions (s) Reviewed	NDA 214103, and all the submitted CMC amendments

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Monica Cooper	OPQ/ONDP/DNDAPI/B3
Drug Product/Environmental Assessment (EA)	Dhanalakshmi Kasi	OPQ/ONDP/DNDPIII/NDPB5
Process and Facility	Kumar Janoria	OPQ/OPMA/DMAI/MAB1
Biopharmaceutics	Poonam Delvadia	OPQ/ONDP/DB/BB3
Microbiology	Elizabeth Bearr	OPQ/OPMA/DMAI/MAB1
Post-Marketing	Kris Raman	OPQ/OLDP/DPMAI/PMB3
Application Technical Lead (ATL)	Mohan Sapru	OPQ/ONDP/DNDPIII/NDPB5

RBPM: Grafton Adams; OPQ/OPRO/DRBPMI/RBPMB2

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 214103 OXLUMO (Lumasiran) Injection is recommended for approval. An expiration period of 36 months is granted for the product when stored at 2°C–25°C (36°F–77° F) in the proposed commercial container closure system.

B. Recommendation on Post-Marketing Commitments (PMCs), Agreements, and/or Risk Management Steps, if Applicable

Not applicable.

II. Background

The Applicant, Alnylam Pharmaceuticals, Inc., sought U.S. marketing approval for NDA 214103 in accordance with Section 505(b)(1) of the FD&C Act. The NDA, a rolling submission, has been granted an orphan drug, breakthrough therapy and the rare pediatric disease designations. The proposed product, OXLUMO (lumasiran) Injection, for subcutaneous use, is indicated for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary oxalate levels in pediatric and adult patients. Hyperoxaluria type 1 (PH1) is an ultra-rare, serious, life-threatening, autosomal recessive disorder caused by a deficiency in the hepatic enzyme alanine-glyoxylate aminotransferase (AGT). There are no approved therapies for PH1, and treatment largely consists of medical management or liver/kidney transplantation. Lumasiran, an RNA interference (RNAi) therapeutic, is designed to inhibit HAO1 (glycolate oxidase) mRNA in the liver via the naturally occurring mechanism of RNAi, thereby, reducing the production of the hepatic enzyme glycolate oxidase that is upstream of the AGT defect that causes PH1. The Applicant requested priority review for this NDA.

II. Quality Assessment Summary

A. Drug Substance (Lumasiran Sodium) Quality Summary

The drug substance is the sodium salt of a chemically synthesized double-stranded oligonucleotide that is covalently linked to a ligand (referred to as L96), which contains three N-acetylgalactosamine (GalNAc) residues. The sense strand and the antisense strand contain 21 and 23 nucleotides, respectively. The 3'-end of the sense strand is conjugated to the GalNAc moiety. The structural characterization data adequately support the proposed structure of the drug substance. The drug substance is highly soluble in water.

Manufacturing: The drug substance manufacturing process consists of (b) (4)

(b) (4)

(b) (4) The proposed manufacturing process, controls of materials, critical process parameters and in-process controls are adequate to ensure the quality of the drug substance.

Specification: The drug substance exists in duplex form due to the Watson-Crick base pairing interactions between the complementary base pairs of the sense and antisense strands. The identity of duplex is confirmed by melting temperature (Tm). In addition, ion pairing reversed phase chromatography HPLC (IPRP-HPLC) with ultraviolet (UV) detection is utilized under non-denaturing conditions to confirm that drug substance is in its native duplex form, and to determine the purity of the duplex structure relative to unhybridized single strands and related impurities.

The types of impurities in the drug substance consist of (b) (4) Nonclinical repeat-dose toxicity studies conducted in the rat have been used for the impurity qualifications on the basis that the rat is identified as the more sensitive toxicity test species. Per Agency recommendation, the Applicant has revised drug substance specified impurity limits to not exceed the maximum levels observed in the nonclinical batches. However, for (b) (4), the applicant has proposed alignment of the acceptance limit with the maximum observed long-term clinical stability result. These proposed acceptance limits for specified impurities are acceptable. The proposed specifications for individual elements, based on Option 1 as defined within ICH Q3D, are adequate. No risk of the presence of (b) (4) impurities has been identified in either the drug substance or drug product.

In conclusion the revised release specification for the drug substance, involving testing of critical quality attributes (CQAs), is adequate. The proposed analytical methods are adequately validated.

The stability data support the proposed retest period of (b) (4) months for the drug substance stored at the recommended long-term storage condition of (b) (4) °C.

B. Drug Product {OXLUMO (Lumasiran) Injection}

Product Design, Release Specification and Packaging: Lumasiran drug product is a sterile solution, containing 189 mg/mL lumasiran (equivalent to 200 mg/mL lumasiran sodium), a HAO1(glycolate oxidase)-directed small interfering ribonucleic acid (siRNA) formulated in water for injection. The sterile, preservative-free, colorless to yellow solution for subcutaneous injection is supplied in a single-use Type (b) (4) clear glass vial with a (b) (4) rubber stopper and an aluminum overseal with a flip-off button. The strength of the drug product is expressed based on the active moiety. No novel excipients or excipients of human origin are used in the manufacture of the drug product. The container closure/packaging has been shown to be adequate for the intended purpose. The proposed product release specification, which includes testing the critical quality attributes such as appearance, identity, purity, assay, specified impurities, unspecified impurities, pH (USP <791>), osmolality (USP <785>), particulate matter (USP<788>), bacterial endotoxins (USP<85>), sterility (USP<71>), volume in container (USP <697>), and container closure integrity, is adequate. The drug product purity and impurities are analyzed by non-denaturing IPRP-HPLC UV, (b) (4). The analytical methods have been validated. In compliance with the Agency recommendations, the Applicant agreed to tighten the specified and total impurity limits based on the non-clinical and clinical data for the drug substance.

Manufacturing: (b) (4) The process flow chart appropriately identifies the key process steps, inputs to each process step as well as the in-process controls. Based on the control strategy, including the listed critical material and process parameters, and in-process controls, the proposed manufacturing process is acceptable.

Microbiological Aspects: (b) (4) The information and data provided concerning sterilization, environmental monitoring, process validation and container/closure integrity testing are adequate. Sterility and bacterial endotoxins are tested at release and on stability in accordance with USP <71> and USP <85>, respectively. The product specification meets regulatory expectations for a sterile drug product.

Biopharmaceutics Aspects: The drug production formulation has remained unchanged throughout all nonclinical and clinical studies. The formulation used throughout the clinical program is also intended for commercial production. Hence, no *in vitro* and/or *in vivo* data for bridging or biowaiver request for the proposed Lumasiran Injection, for subcutaneous injection, is needed.

Expiration Date & Storage Conditions: The totality of product stability data supports an expiration period of 36 months for the product when stored at 2°C–25°C (36°F–77° F) in the proposed commercial container closure system.

III. Assessment of Manufacturing Facilities

Due to the current Covid-19 pandemic travel restrictions (a global level 4 travel warning), preapproval inspection (PAI) of the drug substance manufacturing facility (b) (4)) could not be performed. The finalized 'approval' decision for the drug substance manufacturing site is based on a FDASIA 706 record review in lieu of an on-site PAI. Regarding the other listed manufacturing and testing facilities, there are no outstanding cGMP issues and are deemed acceptable. In conclusion, all these listed facilities have been approved based on inspection history and manufacturing experience of the concerned facilities.

IV. Environmental Exclusion

The Applicant's claimed categorical exclusion from the environmental assessment requirements, under 21 CFR Part 25.31(b), is acceptable.

VI. Comparability Protocols

The Comparability Protocol (CP), submitted as part of pre-marketing NDA submission, proposes (b) (4) will be evaluated for their impact to the product CQAs through a risk assessment. Furthermore, any potential impact to product quality, as well as the comparability of the materials (b) (4) , will be assessed through the execution of an analytical comparability study. Analytical results will be evaluated against the commercial specifications and compared against historical test results. In addition, stability data for the drug substance, (b) (4) will be evaluated to ensure similar trending profiles and conformance with the commercial specification. In response to Agency's recommendations, the final commitments from the Applicant are as follows:

- Upon successful completion of the comparability studies, a post-approval submission of the results supporting implementation (b) (4) will be made (b) (4)
- This CP applies to one-time changes being implemented (b) (4) Alnylam commits to not modifying the comparability protocol without prior review and approval by the Agency.
- (b) (4)
- (b) (4)
- Alnylam will not distribute any product manufactured with the changes until all of the criteria in approved CP have been met and the quality unit has approved the implementation of the changes.

Hence, this Comparability Protocol is recommended for approval. (b) (4) (b) (4)

VII. Life Cycle Knowledge Information

On the next page:

Final Risk Assessment

NDA 214103 Lumasiran Injection

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors Affecting CQA**	**Initial Risk Ranking**	**Risk Mitigation**	**Final Risk Evaluation**	**Comments**
Sterility	Formulation Container Closure Process Parameters Scale/Equipment/ Site	**H (High)**	(b) (4)	Acceptable	
Endotoxin Pyrogen	Formulation Container Closure Process Parameters Scale/equipment/ Site	**M (Moderate)**		Acceptable	
Assay (API), Stability	Formulation Container Closure Raw Materials Process Parameters Scale/Equipment/ Site	L (Low)		Acceptable	
Uniformity of Dose - Fill/ Deliverable Volume	Formulation Container Closure Process Parameters Scale/equipment/ site	**L (Low)**		Acceptable	

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors Affecting CQA**	**Initial Risk Ranking**	**Risk Mitigation or Aggravation**	**Final Risk Evaluation**	**Comments**
Osmolality	Formulation Raw materials Process parameters Scale/equipment/ site	L (Low)	(b) (4)	Acceptable	
pH (High)	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L (Low)		Acceptable	
Particulate Matter	Formulation Container Closure Process Parameters Scale/equipment/ site	M (Moderate)		Acceptable	
Leachable Extracts	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L (Low)		Acceptable	
Appearance	Formulation Raw materials Process Parameters Scale/equipment/ site	L (Low)		Acceptable	

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead (ATL) Assessment and Signature

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 214103 OXLUMO (Lumasiran) Injection is recommended for approval. An expiration period of 36 months is granted for the product when stored at 2°C–25°C (36°F–77°F) in the proposed commercial container closure system.

Mohan Sapru, M.S., Ph.D.
Application Technical Lead (ATL)
CMC Lead; Division of Cardiology and Nephrology
CDER/OPQ/ONDP/DNDPIII/NDPB5

Mohan K. Sapru -S

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate with revisions provided below.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	OXLUMO (lumasiran) injection, for subcutaneous use	Adequate
Established name(s)		
Route(s) of administration		
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Injection: (b) (4) in a single-dose vial.	Revised version: Injection: 94.5 mg/0.5 mL in a single dose vial.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Single Dose	Adequate

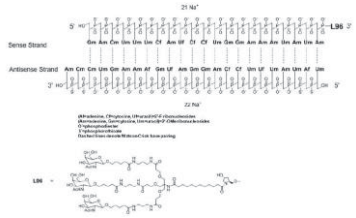
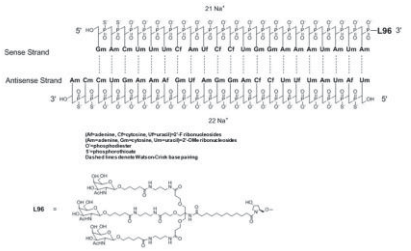
1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	OXLUMO is intended for subcutaneous use by a healthcare professional. (b) (4) OXLUMO is a sterile, preservative-free, clear, colorless-to-yellow solution. It is supplied in a single-dose vial, as a ready-to-use solution that does not require additional reconstitution or dilution prior to administration.	OXLUMO is intended for subcutaneous use and should be administered by a healthcare professional. Visually inspect the drug product solution. Do not use if it contains particulate matter or if it is cloudy or discolored. OXLUMO is a sterile, preservative free, clear, colorless to yellow solution. It is supplied in a single dose vial, as a ready to use solution that does not require additional reconstitution or dilution prior to administration.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Injection: (b) (4) (b) (4) clear, colorless-to-yellow solution in a single-dose vial.	Injection: 94.5 mg/0.5 mL clear, colorless to yellow solution in a single dose vial.
Strength(s) in metric system		
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance		
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting		
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"		
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.		

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s) Dosage form(s) and route(s) of administration If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance. List names of all inactive ingredients. Use USP/NF names. Avoid Brand names. For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol Statement of being sterile (if applicable) Pharmacological/ therapeutic class Chemical name, structural formula, molecular weight If radioactive, statement of important nuclear characteristics. Other important chemical or physical properties (such as pKa or pH)	OXLUMO is a *HAO1*-directed double-stranded small interfering ribonucleic acid (siRNA), covalently linked to a ligand containing (b) (4) *N*-acetylgalactosamine (GalNAc) (b) (4) The structural formula of lumasiran drug substance in its sodium form (b) (4) is presented below:  OXLUMO is supplied as a sterile, preservative-free, clear, colorless-to-yellow solution for subcutaneous (b) (4) (b) (4) sodium hydroxide and/or phosphoric acid to adjust the pH to ~7.0. The molecular formula of lumasiran sodium is $C_{530}H_{669}F_{10}N_{173}O_{320}P_{43}S_6Na_{43}$ and the molecular weight is 17,285.76 Da. (b) (4)	OXLUMO injection contains lumasiran, a *HAO1*-directed double-stranded small interfering ribonucleic acid (siRNA), covalently linked to a ligand containing *N*-acetylgalactosamine (GalNAc). The structural formula of lumasiran sodium is presented below:  The molecular formula of lumasiran sodium is $C_{530}H_{669}F_{10}N_{173}O_{320}P_{43}S_6Na_{43}$ and the molecular weight is 17,285.76 Da. OXLUMO is supplied as a sterile, preservative-free, clear, colorless-to-yellow solution for subcutaneous administration containing the equivalent of 94.5 mg of lumasiran (provided as lumasiran sodium) in 0.5 mL of water for injection and sodium hydroxide and/or phosphoric acid to adjust the pH to ~7.0.

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	None.	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	None.	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) Strength(s) in metric system Available units (e.g., bottles of 100 tablets) Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	OXLUMO (lumasiran) is a clear, colorless-to-yellow (b) (4) solution available in single-dose vials of (b) (4) in cartons containing one vial (NDC 71336-1002-1). Store at 2°C to (b) (4)°C (36°F to (b) (4)°F). Store OXLUMO in its original container until ready for use.	OXLUMO is a clear, colorless-to-yellow solution available in single-dose vials of 94.5 mg/0.5 mL in cartons containing one vial (NDC 71336-1002-1). Store at 2°C to 25°C [36°F to 77°F]. Store OXLUMO in its original container until ready for use.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"		
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.		

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	N/A	
If the product contains a desiccant, ensure the size		

and shape differ from the dosage form and desiccant has a warning such as “Do not eat.”	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	See above.	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “Not made with natural rubber latex. Avoid statements such as “latex-free.”	N/A	
Include information about child-resistant packaging	No Information included.	

1.2.3 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor’s Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured for: Alnylam Pharmaceuticals, Inc., Cambridge, MA 02142 Manufactured by: Vetter Pharma-Fertigung GmbH & Co. KG, Eisenbahnstrasse 2-4, 88085 Langenargen, Germany	Adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

No Information included.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

3.2 Carton Labeling

Assessment of Carton and Container Labeling: *Adequate*

Recommendation: We recommend revising

1. "Subcutaneous use" to read "For Subcutaneous Injection Only"
2. Revise the side panel labeling, "(b) (4)…" to read: "Each 0.5 mL of solution contains 94.5 mg lumasiran (as 100 mg lumasiran sodium) per vial."

These two comments were already addressed by DMEPA team through information request.

Overall Assessment and Recommendation:

The labeling/labels will be adequate from a quality perspective after the recommended changes have been made.

Dhanalakshmi Kasi

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David Claffey

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BIOPHARMACEUTICS REVIEW MEMO Office of New Drug Products		
Application No.	NDA-214103-ORIG-1	
Applicant	Alnylam Pharmaceuticals, Inc.	
Product Name	Oxlumo (lumasiran) injection, for subcutaneous use	
Dosage Form/Strengths	Injection, 189mg/mL	
Route of Administration	Subcutaneous	
Indication	OXLUMO is a HAO1-directed small interfering ribonucleic acid (siRNA) indicated for the treatment of primary hyperoxaluria type 1 (PH1) in pediatric and adult patients [1]	
Submission Date(s)	CMC submission dated 04/03/2020 (Rolling submission)	
Type of Submission	505(b)(1)	
Assignment Date	04/17/2020	
Review Date	07/22/2020	
Due Dates	**Review**	**PDUFA**
	08/25/2020	12/03/2020
Primary Reviewer	Poonam R. Delvadia, Ph.D.	
Secondary Reviewer	Kimberly Raines, Ph.D.	
Biopharmaceutics Branch Chief	Kimberly Raines, Ph.D.	
Biopharmaceutics Division Director	Paul Seo, Ph.D.	
Key Review Point	**Biopharmaceutics Assessment is not needed for this NDA (See details below)**	

This 505(b)(1) application seeks approval for Lumasiran Injection. Lumasiran is an RNA interference (RNAi) therapeutic, designed to reduce hepatic oxalate production and thereby reduce urinary and plasma oxalate levels in Primary Hyperoxaluria Type 1 (PH1) pediatric and adult patients. PH1 is a rare progressive, serious and life-threatening autosomal recessive inborn error of metabolism. Lumasiran has been granted Orphan Drug, Breakthrough Therapy and Priority Review designations.

The proposed product is a sterile solution, containing 189 mg/mL lumasiran (equivalent to 200 mg/mL lumasiran sodium), a double-stranded small interfering ribonucleic acid (siRNA), formulated in water for injection.[2] The formulation is supplied in a single dose vial. Each vial contains 0.5 mL nominal volume of lumasiran solution (equivalent to 94.5 mg of lumasiran i.e., 100mg of lumasiran sodium. The proposed composition is presented in Table 1.

[1] \\cdsesub1\evsprod\nda214103\0020\m1\us\114-labeling\draft\labeling\oxlumo-lumasiran-us-prescribing-information-pdf.pdf (Accessed on 07/22/2020)
[2] \\cdsesub1\evsprod\nda214103\0006\m3\32-body-data\32p-drug-prod\lumasiran-injection-all\32p1-desc-comp\description-and-composition.pdf (Accessed on 07/22/2020)

Table 1: Composition of Lumasiran Drug Product

Component	Concentration (mg/mL)	Content per Vial (mg)	Function	Quality Standard
Lumasiran drug substance (Lumasiran sodium)	200 [a]	100 [b]	Active ingredient	Manufacturer's specifications
Water for Injection	QS	QS	Diluent	USP-NF, Ph. Eur., JP
Phosphoric acid [c]	QS [d]	QS [d]	pH adjustment agent	USP-NF, Ph. Eur., JP
Sodium hydroxide [c]	QS [d]	QS [d]	pH adjustment agent	USP-NF, Ph. Eur., JP

[a] equivalent to 189 mg/mL lumasiran

[b] equivalent to 94.5 mg lumasiran

[c] pH adjustment agents are added only if needed (refer to 3.2.P.3.3 Description of Manufacturing Process and Process Controls for information)

[d] QS to target pH 7.0

Abbreviations: QS=Quantum satis; Ph. Eur.=European Pharmacopoeia; USP-NF=United States Pharmacopeia-National Formulary; JP=Japanese Pharmacopoeia

The Applicant has conducted three in vivo studies (ALN-GO1-001 Part A and B, ALN-GO1-002, ALN-GO1-004) that evaluated pharmacokinetics of lumasiran. These studies will be assessed by the Office of Clinical Pharmacology (OCP). The following is noted in M 3.2.P.2.2 "The DP formulation has remained unchanged throughout all nonclinical and clinical studies."[3] The same formulation is used throughout the clinical program and is intended commercial formulation. Therefore, any in vitro and/or in vivo data for bridging or biowaiver request for the proposed Lumasiran solution for subcutaneous injection is not needed.

Based on the biopharmaceutics filing assessment,[4] there are no biopharmaceutics information that needs to be assessed by the Division of Biopharmaceutics, ONDP for this NDA.

[3] \\cdsesub1\evsprod\nda214103\0006\m3\32-body-data\32p-drug-prod\lumasiran-injection-all\32p2-pharm-dev\pharmaceutical-development-formulation.pdf (Accessed on 07/22/2020)

[4] https://panorama fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f883e84abe (Accessed on 07/22/2020)

Poonam Delvadia

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Kimberly Raines

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	A small siRNA for treatment of primary hyperoxaluria type 1 (PH1) in pediatric and adult patients.
NDA Number	214103
Assessment Cycle Number	1
Drug Product Name/ Strength	Oxlumo (lumasiran; ALN-GO1)
Route of Administration	(b) (4)
Applicant Name	Alnylam Pharmaceuticals
Therapeutic Classification/ OND Division	Rare Pediatric Disease Priority Review
Manufacturing Site	Vetter Pharma-Fertigung GmbH & Co. KG Eisenbahnstrasse 2-4 88085 Langenargen Germany
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary: The (b) (4) . The product-contact equipment is sterilized by (b) (4) . Vials are (b) (4) .

List Submissions being assessed (table):

Document(s) Assessed	Date Received
006 (6)	04/03/2020
0010 (11)	05/21/2020
0013 (13)	06/04/2020
0017 (19)	07/07/2020
0022 (22)	07/23/2020
0024 (24)	08/18/2020

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: This is a rolling submission with clinical information submitted January 10, 2020 and the CMC information submitted April 3, 2020. An initial IR requesting the large portions of information missing in the submission was

sent April 24, 2020 with responses dated May 21, 2020. Additional IRs were sent on May 21, 2020 with response dated June 4, 2020 and June 22, 2020 with a response dated July 7, 2020.
A comparability protocol was submitted for (b) (4)

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): N/A

Supporting Documents: Review of n (b) (4) mr01.docx on 11/17/2016 for (b) (4) information. Review of DMF (b) (4) in D (b) (4) M17R01.docx on June 16, 2020.

The submission dated 4/3/2020 is lacking large portions of information. This general deficiency was sent in an information request dated 4/24/2020.

Deficiency (April 24, 2020): Please note that the subject NDA is lacking substantial documentation of sterilization validation information. Please refer to FDA's 1994 Guidance document "Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" for documentation recommendations when you are preparing your responses to microbiology information requests. (https://www.fda.gov/media/71442/download)

Response from the Applicant (May 21, 2020): 1.11.1 Responses to CMC IR Received 24Apr2020.pdf
The applicant acknowledges the Agency's comment and provided additional information.

S DRUG SUBSTANCE

The drug substance is supplied (b) (4) .

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

(3.2.P.1 Description and Composition of the Drug Product.pdf)

- **Description of drug product –** Lumasiran is a preservative-free, colorless to yellow solution with pH 7.0. This is a sterile, single-use product filled into (b) (4), type (b) (4) glass vials with a 0.5 mL fill and is administered subcutaneously.
- **Drug product composition –**

Ingredient	Function	Quantity mg/mL
Lumasiran drug substance (Lumasiran sodium)	API	200*
Water for Injection	Diluent	q.s.
Phosphoric Acid	pH adjustment agent	q.s.
Sodium Hydroxide	pH adjustment agent	q.s.

* equivalent to 189 mg/mL lumasiran

Description of container closure system –

- (b) (4) amber type (b) (4) glass 3 mL vials
- 13 mm (b) (4) stoppers
- 13 mm tear off aluminum seal, green (b) (4) cap

Note to Reviewer: Letter of authorizations for DMFs related to the container closure system are provided. It indicates that the vials are obtained from (b) (4) and the stoppers are obtained from (b) (4) .

Reviewer's Assessment:
The description of the drug product is adequate, however, there is no information pertaining to the manufacturer of the container closure system.

Deficiency (May 21, 2020): The proposed use of a (b) (4) type (b) (4) glass vial with 13 mm (b) (4) stopper and 13 mm tear off aluminum seal with green (b) (4) cap for the subject drug product is acknowledged. Provide the name and address of the manufacturer(s) of the vial, stopper, and seal.

Response from the Applicant (June 4, 2020): 1.11.1 Responses to CMC IR Received on 21MAY2020.pdf)

Component	Name	Address
Vial	(b) (4)	
Stopper		

Seal	(b) (4)

Reviewer's Assessment: ***Adequate***
The description of the drug product and CCS is adequate.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

(3.2.P.2 microbiological-attributes.pdf)

(b) (4)

62 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MOHAN K SAPRU
10/30/2020 09:47:06 PM