CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215842Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	215842		
Applicant Name	Novo Nordisk, Inc.		
Drug Product Name	Rifloza (nedosiran)		
Dosage Form.	Injection		
Proposed Strength(s)	• 160 mg (1 mL) single-dose Pre-filled Syringe (PFS) • 128 mg (0.8 mL) single-dose PFS • 80 mg (0.5 mL) single-dose vial		
Route of Administration	Subcutaneous		
Maximum Daily Dose	160 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Treatment of Primary Hypoxaluria Type 1 (PH1)		
Drug Product Description	Nedosiran is supplied as a 160 mg (1 mL) single-dose PFS, a 128 mg (0.8 mL) single-dose PFS, and an 80 mg (0.5 mL) single-dose vial.		
Co-packaged product information	N/A		
Device information:	The container closure is a prefilled syringe for two of the drug products.		
Storage Temperature/ Conditions	2°C to 8 °C. Store in original carton, away from direct heat and light.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Daniel Jansen OPQ/ONDP/DNDAPI/NDB3	Zhengfu Wang OPQ/ONDP/DNDAPI/NDB3
	Drug Product/ Labeling	Dan Berger OPQ/ONDP/DNDPIII/NDPB5	Mohan Sapru OPQ/ONDP/DNDPIII/NDPB5

	Manufacturing	Zhouxi Wang OPQ/OPMA/DPMAIII/PMB9	Kamal Tiwari OPQ/OPMA/DPMAIII/PMB9
	Biopharmaceutics	N/A	
	Microbiology	BreOnna DeLaine-Elias OPQ/OPMA/DMAI/MAB2	Neal Sweeney OPQ/OPMA/DMAI/MAB2
	Other (specify):	N/A	
	RBPM	Grafton Adams OPQ/OPRO/DRBPMI/RBPMB2	
	ATL	Theodore Carver OPQ/ONDP/DNDPIII/NDPB5	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

A shelf life of 36 months is granted for the drug product in a glass vial (0.5 mL) when stored at 2ºC to 8ºC. A shelf life of 30 months is granted for the drug products in prefilled syringes (0.8 mL and 1.0 mL) when stored at 2ºC to 8ºC.

b. Additional Comments for Action: None.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1.) Background

The Applicant, Novo Nordisk, Inc., seeks marketing approval for nedosiran, a synthetic, double-stranded RNA nucleotide conjugated to N-acetyl-D-galactosamine (GalNAc) amino sugar residues, in accordance with Section 505(b)(1) of the FD&C Act. Nedosiran is a hepatic LDH-directed small interfering RNA proposed for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary oxalate levels in pediatric (9 years of age and older) and adult patients with relatively preserved kidney function. Nedosiran is a

new molecular entity and has been granted orphan drug status. The OPQ review of Rifloza(nedosiran) injection included drug substance, drug product, manufacturing, and microbiology reviews.

2.) Drug Substance

The nedosiran drug substance is a double-stranded RNA conjugated to N-acetyl-D-galactosamine (GalNAc) amino sugar residues. The sense strand contains 36 nucleotides, and the antisense strand contains 22 nucleotides. The drug substance review concluded that the physicochemical characteristics and structure of the drug substance have been appropriately characterized. The nedosiran drug substance is manufactured (b) (4) . In response to information requests, the Applicant included a melting temperature test to confirm identity of the duplex and an additional chromatographic method, anion exchange HPLC, to monitor impurities in the drug substance specification. For monitoring nedosiran-related substances, the following methods are included in the specification: non-denaturing SAX-HPLC, denaturing IP-RP-UHPLC, and denaturing AX-HPLC. The proposed re-test period of (b) (4) months was determined to be supported by real-time stability data provided for three batches of the drug substance.

3.) Drug Product

Rivfloza (Nedosiran) for subcutaneous injection is a sterile solution containing the equivalent of 160 mg/mL of nedosiran (supplied as 170 mg/mL of nedosiran sodium) and provided in three presentations: a 0.5 mL solution in a glass vial and 0.8 mL and 1.0 mL solutions in the same pre-filled syringe. The drug substance is dissolved in WFI, with no excipients in the formulation other than sodium hydroxide and hydrochloric acid, which may be added to adjust pH. The drug product in vials is packaged in a (b) (4) clear glass vial that is sealed with a (b) (4) rubber stopper and secured with an aluminum cap with a flip-off plastic button. The pre-filled syringes consist of (b) (4) glass barrels, stainless steel (b) (4) staked needles, and (b) (4) rubber plungers. The drug product is stored in the secondary carton until use due to light sensitivity. The drug product specification was found to include appropriate methods for controlling the identity, content, and purity of the drug product. Similar to the drug substance specification, the following methods are included in the drug product specification for testing for related substances: non-denaturing SAX-HPLC, denaturing IP-RP-UHPLC, and denaturing AX-HPLC. The stability data provided support the proposed shelf-life of 36 months when stored at 5°C in vials and 30 months at 5°C for the 0.8 mL and 1.0 mL solutions stored in the PFS, with room temperature storage

allowed for up to 28 days prior to administration (defined in the label as 15°C to 30°C).

4.) Manufacturing

Process - The proposed commercial drug product manufacturing process is (b) (4) . The target fill volumes for the PFS presentations are (b) (4) mL and (b) (4) mL, to provide deliverable volumes of 0.8 and 1.0 mL, respectively. The review determined that the drug product manufacturing process is adequate.

Facilities - All the listed manufacturing facilities are approvable (from OPMA standpoint, concurred by ORA) based on the firm's PAI, inspection history and manufacturing experience.

5.) Microbiology

After review of the NDA and the Applicant responses to information requests regarding the environmental monitoring, (b) (4) and equipment validation, filling times, and container closure integrity testing, the information in the NDA was deemed adequate from the microbiological perspective. The proposed shelf life and in-use period were determined to be supported from the microbiology perspective. The applicant submitted a comparability protocol for the addition of an alternate sterilization method and site for the PFS plunger. This protocol was reviewed and found to be adequate.

6.) Quality Labeling

The quality labeling was reviewed and found to be adequate after final revisions, including changes communicated to the Applicant.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**N/A**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments: None.

Comparability Protocols (PACMP): Yes
Comments:
The comparability protocol for the addition of an alternate sterilization method and site for the PFS plunger was reviewed and is approved (see microbiology review).

(b) (4)

Additional Lifecycle Comments: See above comment regarding information to be included in a future comparability protocol.

Theodore Carver

Digitally signed by Theodore Carver
Date: 6/11/2023 09:40:21PM
GUID: 5d963967007fd4bc3c9fab2a6c3eaded

81 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

Following edits made to sections 3, 11 and 16, the prescribing information meets all regulatory requirements from a CMC perspective.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	TRADE NAME	Adequate
Established name(s)	Nedosiran	Adequate
Route(s) of administration	For injection	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	160 mg (1 mL) single-dose PFS, 128 mg (0.8 mL) single-dose PFS 80 mg (0.5 mL) single-dose vial	Product strength expressed in terms of the active moiety per USP salt policy is adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	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 pre-filled syringe. Single-dose vial	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)	NA	NA

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	Adequate
Strength(s) in metric system	160 mg/mL: 160 mg (1.0 mL) PFS 128 mg (0.8 mL) PFS 80 mg (0.5 mL) vial	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Injection 160 mg/mL (present as 170 mg nedosiran sodium salt)	Adequate, after edits made (per the USP Salt Policy)
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Clear, colorless-to-yellow solution	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
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.	Single-dose	Adequate

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	BRANDNAME, nedosiran	Adequate
Dosage form(s) and route(s) of administration	Pre-filled Syringe for subcutaneous injection, vial for subcutaneous injection.	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	NA	NA
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Water for injection, sodium hydroxide and/or hydrochloric acid to adjust pH	Adequate
For parenteral injectable dosage forms, include name and quantities of all inactive ingredients.	NA (pH adjusting excipients are not required).	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Statement of being sterile (if applicable)	Present	Adequate
Pharmacological/ Therapeutic class	Targets lactate dehydrogenase A (LDHA)	Adequate
Chemical name, structural formula, molecular weight	Chemical name NA (double-stranded RNA compound), $C_{662}H_{808}F_{19}N_{231}O_{413}P_{57}S_6Na_{57}$, 22,238 Da.	Adequate
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	Freely soluble in water.	Adequate, after edits made

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	NA
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	NA	NA

1.2.4 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)	Pre-filled Syringes and single-dose vials	Adequate
Strength(s) in metric system	160 mg per mL	Adequate
Available units (e.g., bottles of 100 tablets)	PFS: 160 mg/1 mL PFS: 128 mg/0.8 mL Vial: 80 mg/0.5 mL	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Clear, sterile, preservative-free, colorless-to-yellow solution, NDC 0169-5306-10, 0169-5307-08, 0169-5308-01.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	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 Pre-filled Syringe Single-dose vial	Adequate

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.)	Do not freeze. Store in original carton, away from direct heat and light.	Adequate
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."	NA	NA
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store refrigerated at 2°C to 8°C (36°F to 46°F). TRADENAME can be stored, if needed, at 15°C to 30°C (59°F to 86°F) for a maximum of 28 days (4 weeks).	Adequate, with edits made
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."	NA	NA
Include information about child-resistant packaging	NA	NA

1.2.5 Other Sections of Labeling

No other sections of the labeling contain product quality information.

1.2.6 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 by Pyramid Laboratories 3598 Cadillac Ave Costa Mesa, CA 92626	Adequate.

2.0 PATIENT LABELING

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

Storage conditions, handling instructions and inactive ingredient list are provided in the Patient Information and Instructions for Use. After inclusion of edited storage conditions, this information complies with all regulatory requirements from a CMC perspective.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

Vial

Pre-Filled Syringe (PFS)

3 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Information Provided in the NDA	Assessor's Comments about vial, PFS and carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Rivfloza (nedosiran)	Adequate
Dosage strength	160 mg/mL	Adequate
Route of administration	For subcutaneous injection only	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Each vial contains 80 mg nedosiran (equivalent to 85 mg nedosiran sodium)	Adequate for both vial and PFS cartons, following recommended edits to be incorporated by the Applicant
Net contents (e.g. tablet count)	1 x 0.5 mL vial or 1 x 0.8 mL (or 1 mL) PFS	Adequate
"Rx only" displayed on the principal display	Present	Adequate
NDC number	Present	Adequate
Lot number and expiration date	Present	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store between 2°C and 8°C (36°F and 46°F), at 15°C to 30°C (59°F to 86°F) for no longer than 28 days (4 weeks).	Adequate, following edits made.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Single-dose vial Single-dose Pre-filled Syringe	Adequate
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Bar code	Present	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Bottle Labeling
Name of manufacturer/distributor	Manufactured by PYRAMID Laboratories, Inc., Costa Mesa, CA 92626 USA for Dicerna Pharmaceuticals	Adequate
Medication Guide (if applicable)	NA	NA
No text on Ferrule and Cap overseal	NA	NA
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	NA	NA
Additional carton labeling comment	The following IR has been sent: The salt equivalence statement on your carton labels is improperly placed following the description of inactive ingredients. For the carton labels, amend the drug product description for your vials and pre-filled syringes as applicable: "Each Pre-filled Syringe (*or vial*) contains # mg of nedosiran in # mL of water (equivalent to # mg of nedosiran sodium), with sodium hydroxide and/or hydrochloric acid added to adjust the pH to ~ 7.2 for injection."	Adequate for both vial and PFS cartons, following recommended edits to be incorporated by the Applicant

Assessment of Carton and Container Labeling: *Adequate*

Required edits have been agreed to by the Applicant regarding the storage information. Additionally, the Applicant has been advised of further corrections to apply to the carton drug product description/salt equivalence statement. With the required edits, the labels comply with all regulatory requirements from a CMC perspective.

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

All edits to the carton and container labels have been completed or are currently addressed. The Prescribing Information, Patient Information, Instructions for Use and labels comply with all regulatory requirements from a CMC perspective.

Primary Labeling Assessor Name and Date:

Dan Berger, Ph.D. May 26, 2023

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Mohan Sapru, Ph.D. May 26, 2023

Dan Berger

Digitally signed by Dan Berger
Date: 5/26/2023 02:14:10PM
GUID: 56e6e1b5001a2fedae663c62a5ce7513

Mohan Sapru

Digitally signed by Mohan Sapru
Date: 5/26/2023 02:33:14PM
GUID: 504f821600000ec6d20b59d2b68eb3d2

40 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	Nedosiran sodium is indicated for the treatment of primary hyperoxaluria Type 1
NDA Number	215842
Assessment Cycle Number	01
Drug Product Name/ Strength	Rivfloza (Nedosiran sodium), 170 mg/mL 0.5 mL fill in single-dose 2 mL vial 1.0 mL and 0.8 mL fill in a 1.0 mL syringe
Route of Administration	Subcutaneous Injection
Applicant Name	Novo Nordisk, Inc. P.O. Box 846, Plainsboro, NJ 08536
Therapeutic Classification/ OND Division	DCN
Manufacturing Site	PYRAMID Laboratories, Inc. 3598 Cadillac Avenue Costa Mesa, CA 92626 FEI No. 1000160734
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary**:** The submission **is recommended** for approval on the basis of sterility assurance.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
SN 0001 (pre-submission, part 1)	March 31, 2022
SN 0002 (pre-submission, part 2 with CMC data)	May 31, 2022
SN 0003 (final submission, part 3 with CMC data)	September 30, 2022
SN 0013 (IR response, batch analysis data)	January 31, 2023
SN 00017 (IR response, batch analysis data)	March 28, 2023
SN 0030 (IR response to microbiology IR)	May 15, 2023

Highlight Key Issues from Last Cycle and Their Resolution: N/A. This is a first cycle review.

Remarks: This NDA application is submitted as a 505(b)(1) rolling submission submitted by Dicerna Pharmaceuticals, Inc. (a subsidiary of Novo Nordisk, the applicant). Reference is made to the original IND 132214 submitted by Dicerna on February 26, 2018 for nedosiran, in which the applicant requested feedback regarding the submission of an NDA.

23 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

MICROBIOLOGY LIST OF DEFICIENCIES

NDA: 215842 APPLICANT: Novo Nordisk, Inc.

DRUG PRODUCT: Rivfloza (Nedosiran sodium), 170 mg/mL

There are currently no deficiencies identified based on the information submitted.

Primary Microbiology Assessor Name and Date:
BreOnna DeLaine-Elias, Ph.D.
Microbiologist
CDER/OPQ/OPMA/DMA 1/Branch 2
May 21, 2023

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Neal J. Sweeney, Ph.D.
Senior Pharmaceutical Quality Assessor
CDER/OPQ/OPMA/DMA 1/Branch 2
May 21, 2023

Neal Sweeney

Digitally signed by Neal Sweeney
Date: 5/22/2023 10:50:49AM
GUID: 508da70c00028f5119acd77351f33159

BreOnna DeLaine-Elias

Digitally signed by BreOnna DeLaine-Elias
Date: 5/22/2023 09:53:17AM
GUID: 5ac25343000d65c2cf1465565c19a22f

Theodore Carver

Digitally signed by Theodore Carver
Date: 6/11/2023 10:21:37PM
GUID: 5d963967007fd4bc3c9fab2a6c3eaded

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/

THEODORE E CARVER
06/11/2023 10:35:20 PM