CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217388Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number	217388		
Applicant Name	Ionis Inc.		
Drug Product Name	TRADENAME (eplontersen)		
Dosage Form	Injection		
Proposed Strength(s)	45 mg/0.8 mL		
Route of Administration	Subcutaneous		
Maximum Daily Dose	45 mg administered once monthly		
Rx/OTC Dispensed	Rx		
Proposed Indication	Treatment of the polyneuropathy of hereditary transthyretin mediated amyloidosis (ATTRv) in adults		
Drug Product Description	clear, colorless-to-yellow solution in a single-dose autoinjector		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	(b) (4) (b) (4) Refrigerate, 2°C to 8°C. Patient/caregiver may store at up to 30°C/6 weeks if needed.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Katherine Duncan	Donna Christner
	Drug Product	Jizhou Wang	Martha Heimann
	Labeling	Jizhou Wang	Martha Heimann
	Manufacturing	Raeann Wu	Cassandra Abellard
	Biopharmaceutics	N/A	N/A
	Microbiology	Helen Ngai	Elizabeth Bearr

	Environmental:	N/A	N/A
	RBPM	Erica Keafer	
	ATL	Martha Heimann	
Consults	Alan Stevens (CDRH/OPEQ) reviewed device aspects of the product (autoinjector and syringe). His review, dated 8/22/2023, recommends approval of the application.[1]		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

24 months when stored refrigerated, 2°C to 8°C.

b. Additional Comments for Action

There are no additional comments for the action letter.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The Office of Pharmaceutical Quality (OPQ) recommends **APPROVAL** of NDA 217388 for TRADENAME (eplontersen injection). Based on our evaluation of the available information, the applicant provided sufficient information to support an approval recommendation from the product quality perspective. The applicant provided adequate information to ensure the identity, strength, purity, and strength of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. Minor revisions to the proposed labeling and labels will be made when the clinical division initiates labeling negotiations with the applicant.[2] The proposed labeling is otherwise adequate to meet the regulatory requirements.

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

Recommendation by Subdiscipline:

Drug Substance - Adequate
Drug Product - Adequate

[1] https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af806ecb99&showAsPdf=true
[2] Refer to the Labeling Review for further details.

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:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:

There are no outstanding issues or lifecycle considerations.

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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:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	proposed (b) (4) for review	Defer to DMEPA
Established name(s)	eplontersen	Adequate
Route(s) of administration	Subcutaneous	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	45 mg/0.8 mL in a single-dose autoinjector	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
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.	Yes 45 mg/0.8 mL in a single-dose autoinjector	Adequate

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

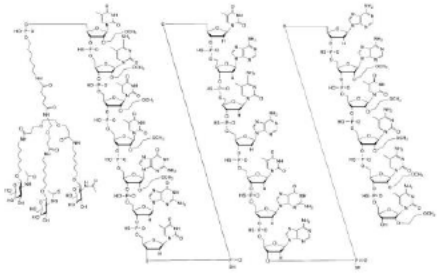
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	N/A

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	45 mg administered by subcutaneous injection once monthly	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	45 mg eplontersen (equivalent to 47 mg eplontersen sodium)	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	A sterile, preservative-free, aqueous solution for subcutaneous injection	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
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.	Include " 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)	Eplontersen	Adequate
Dosage form(s) and route(s) of administration	A sterile, preservative-free, aqueous solution for subcutaneous injection	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	45 mg eplontersen (equivalent to 47 mg eplontersen sodium)	Adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	The solution also contains (b) (4) (b) (4) and may include hydrochloric acid and/or sodium hydroxide for pH adjustment (b) (4) 6.9-7.9	Inadequate
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.	Each single-dose autoinjector contains 45 mg eplontersen (equivalent to 47 mg eplontersen sodium) in 0.8 mL of solution. The solution also contains (b) (4) (b) (4) and may include hydrochloric acid and/or sodium hydroxide (for pH adjustment (b) (4) 6.9-7.9.)	Inadequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Statement of being sterile (if applicable)	Yes	Adequate
Pharmacological/therapeutic class	Eplontersen is an antisense oligonucleotide (ASO) (b) (4)	Adequate

	(b) (4) (b) (4) covalently linked to a ligand containing three N-acetyl galactosamine (GalNAc) residues to enable delivery of the ASO to hepatocytes	
Chemical name, structural formula, molecular weight	Missing chemical name  Molecular formula: C296H417N77O156P20S13Na20 and the molecular weight = 9046.1 Da.	**Inadequate**
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	pH is 6.9-7.9	Adequate

Section 11 (DESCRIPTION) Continued

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

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)	autoinjector	Adequate

Strength(s) in metric system	0.8 mL of solution containing 45 mg of eplontersen	Adequate
Available units (e.g., bottles of 100 tablets)	Each carton contains one 45 mg single-dose autoinjector	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC: 0310-9400-01.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
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

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.)	Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton protected from light. Do not freeze. Do not expose to heat.	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."	N/A	Adequate
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	Adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber	Not provided	Inadequate

latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."		
Include information about child-resistant packaging	N/A	N/A

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they 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		
Distributed by:	AstraZeneca Pharmaceuticals LP Wilmington, DE 19850	Adequate

2.0 PATIENT LABELING

N/A

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

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CARTON AND CONTAINER LABELING

3.1 & 3.2. Container and Carton Label

Container label:

2 Page(s) 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 Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	eplontersen	Adequate
Dosage strength	45 mg/0.8 mL	Adequate
Route of administration	Subcutaneous injection	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	45 mg eplontersen (equivalent to 47 mg eplontersen sodium).	Adequate
Net contents (e.g. tablet count)	0.8 ml	Adequate
"Rx only" displayed on the principal display	yes	Adequate
NDC number	NDC 0310-9400-01	Adequate
Lot number and expiration date	yes	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton protected from light. Do not freeze. Do not expose to heat.	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	single-dose	Adequate
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Bar code	Yes	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Yes	Adequate
Medication Guide (if applicable)	Yes	Adequate
No text on Ferrule and Cap overseal	N/A	N/A
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.	N/A	N/A
And others, if space is available	N/A	N/A

Assessment of Carton and Container Labeling: ***Inadequate***

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

1. Include the chemical name of the drug substance in Section 11 (DESCRIPTION) of labeling.
2. Provide quantities for all the inactive ingredients in Section 11 (DESCRIPTION) of labeling and on container labels. Alternatively, provide a statement that they are buffer solution or used for adjusting the pH.
3. Adopt USP-NF names for all the inactive ingredients and alphabetize them in Section 11 (DESCRIPTION) of labeling. The same applies to container labels.

Overall Assessment and Recommendation:

Primary Labeling Assessor Name and Date:
Secondary Assessor Name and Date (and Secondary Summary,

APPEARS THIS WAY ON ORIGINAL

Jizhou Wang

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Martha Heimann

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U.S. FOOD & DRUG ADMINISTRATION

NDA 217388
Assessment # 01

CHAPTER VII: MICROBIOLOGY

For more details about the items in this template, please see Chapter VII (Microbiology) of the ANDA IQA Guide

Product Information	505(b)(1)
NDA Number	217388
Assessment Cycle Number	MR01
Drug Product Name / Strength	Established name: eplontersen. Proprietary name: not assigned yet. Strength: 56 mg/ mL.
Route of Administration	subcutaneous
Applicant Name	Ionis Pharmaceuticals, Inc.
Manufacturing Site	(b) (4)
Method of Sterilization	

Assessment Recommendation: **Adequate**

Theme:

☐ N/A	☐ Depyrogenation Validation Data
☐ Product Sterility Assurance	☐ Product Release and/or Stability Specifications
☐ Media Fill Data	☐ Validation for Product Release and/or Stability Test Method
☐ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: *(Click link to view Justification Statements)*

N/A
Other (Requires Division Director Approval) – Assessor writes justification here if "other" selected as theme.

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

List Submissions Being Assessed:

Document(s) Assessed	Date Received
Orig 1 (SD 1)	12/22/2022
Orig 1 (SD 10)	4/13/2023

Highlight Key Issues from Last Cycle and Their Resolution:

Remarks: The internal goal dates are: 74 day letter: 3/6/2023. The CMC mid cycle is 5/16/2023, OND mid cycle meeting is 5/22/2023. The microbiology IR was issued 3/30/2023; response received 4/13/2023. PDUFA date is 12/22/2023.

Concise Description of Outstanding Issues : none

Supporting Documents:

Type V DMF (b) (4) for the (b) (4) (b) (4) LOA date (b) (4) Relevant information is referenced to DMA review D(b) (4)M98R01.docx (adequate, dated 3/8/2023) and D(b) (4)M76R01. pdf (adequate, dated 11/3/2020).

Type V DMF (b) (4) for the (b) (4) (b) (4) LOA date (b) (4) Relevant information is referenced to DMA review D (b) (4)M09R01.pdf (adequate dated 6/27/2022).

Type V DMF (b) (4) for the (b) (4) (b) (4) LOA date (b) (4). Relevant information is referenced to DMA review D (b) (4)M25R01.docx (adequate, dated 3/8/2023).

Type V DMF (b) (4) for the (b) (4) (b) (4) LOA date (b) (4) Relevant information is referenced to DMA review D (b) (4)M42R01.docx (adequate, dated 3/24/2023).

Type V DMF (b) (4) for the (b) (4) (b) (4) LOA date (b) (4). Relevant information is reference to DMA review D (b) (4)M11R01.docx (adequate, dated 4/13/2022).

DMA review N (b) (4)MR01.pdf (adequate, dated 12/1/2021). The review is referenced for the same manufacturing facility, area (b) (4) similar container closure system (b) (4) (b) (4) (b) (4) and environmental monitoring program.

DMA review N (b) (4)MR01.docx (adequate, dated 3/17/2023). The review is referenced for the same manufacturing facility, area (b) (4) similar

container closure system [redacted]

Select Number of Approved Comparability Protocols: 0

S DRUG SUBSTANCE

S.2. Manufacture

S.2.1 Manufacturers – [redacted] Responsibilities: manufacture, quality control testing, release, stability.

Assessment: **Adequate**

S.4 Control of drug substance

S.4.1 Specification – Bacterial endotoxins: NMT [redacted] EU/mg. Total aerobic microbial count: NMT [redacted] CFU/g. Total yeast/ mold count: NMT [redacted] CFU/g.

Assessment: **Adequate**. The limits concur with USP <1111>.

P Drug Product

P.1 Description of the composition of the drug product

- Description of drug product –

(12/22/2022, 3.2.P.1., *description-and-composition.pdf*)

The drug product is a clear and colorless to yellow, sterile, preservative free, parenteral solution intended for subcutaneous (SC) administration. Single use, SC injection once monthly.

- Drug product composition –

Ingredient	Quantity per unit dose (0.8 mL)	Function
Eplontersen[a]	45 mg	Active
Sodium Dihydrogen Phosphate Dihydrate[c,d]	[redacted]	[redacted]
Disodium Hydrogen Phosphate Anhydrous[c,e]		
Sodium chloride		Tonicity modifier
Hydrochloric acid	q.s.	pH adjustment
Sodium hydroxide	q.s.	pH adjustment
Water for Injection	q.s. top 0.8 mL	[redacted]

[a] (b) (4) The label claim of 45 mg eplontersen is (b) (4) equivalent to 47 mg of eplontersen sodium.
[c] (b) (4) (b) (4)
[d] Alternative name: monobasic sodium phosphate (dihydrate)
[e] Alternative name: dibasic sodium phosphate (anhydrous)

Exhibit batch size: (b) (4) grams, ~ (b) (4) autoinjectors.
Maximum proposed commercial batch size: (b) (4) liters (~ (b) (4) autoinjectors)

- Description of container closure system –
(12/22/2022, 3.2.P.7., *container-closure-system.pdf*)

Configuration	Component	Description	Manufacturer
Syringe, stopper	Syringe, needle, rigid needle shield	1 mL Long (b) (4) glass, Type (b) (4) clear, compliant with USP <660>, with 27G ½" special thin wall, 5 bevel stainless steel needle and a rigid needle shield. (b) (4) Catalog number (b) (4)	(b) (4)
	Stopper	(b) (4) rubber, (b) (4) grey, compliant with USP <381>. (b) (4) (b) (4)	(b) (4) DMF (b) (4)
	Stopper	(b) (4) rubber, (b) (4) grey, compliant with USP <381>. (b) (4) (b) (4)	(b) (4) DMF (b) (4)

The syringe, needle, shield are purchased (b) (4) from the manufacturer. Stoppers are purchased (b) (4) (b) (4) from the manufacturers.

Additional information: The pre-filled syringe (PFS) is assembled into an autoinjector for the final drug product presentation. The autoinjector is not in direct contact with the sterile drug product.

Assessment: Adequate

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 Microbiological attributes

(b) (4)

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Helen Ngai

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Elizabeth Bearr

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/s/

MARTHA R HEIMANN
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