CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213026Orig1s000

PRODUCT QUALITY REVIEW(S)

FDA U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION: Approval with Post-Marketing Requirement

NDA 213026
Review #1

Drug Product Name	AMONDYS 45™ (casimersen)
Dosage Form	Injection
Strength	50 mg/mL
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Sarepta Therapeutics
US agent, if applicable	N/A

QUALITY TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Katharine Duncan	Donna Christner
Drug Product	Renishkumar Delvadia	Julia Pinto
Manufacturing	Frank Wackes	Joanne Wang
Microbiology	Aditi Das	Neal Sweeney
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Florence Aisida/Erica Keafer	
Application Technical Lead	Martha Heimann	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

Submission(s)	Document Date	Discipline(s) Affected
SD-1, Clinical and nonclinical presubmission	1/10/2020	Manufacturing
SD-8, Original NDA	6/25/2020	All
SD-9, Response to information request (IR)	8/04/2020	Manufacturing
SD-10, Response to IR	8/10/2020	Manufacturing
SD-13, Response to IR	8/17/2020	Manufacturing
SD-15, Response to IR	9/2/2020	Manufacturing

SD-18, Response to IR	9/14/2020	Manufacturing
SD-20, Response to IR	9/25/2020	Manufacturing
SD-23, Response to IR	10/6/2020	Manufacturing
SD-25, Response to IR	11/5/2020	Drug Substance
SD-28, PMR milestone dates	2/9/2021	Drug Product

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QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessed	Comments
(b) (4)	V		(b) (4)	Adequate	N/A	See Note 1
	III			N/A	N/A	See Note 2
	III			N/A	N/A	See Note 2
	III			N/A	N/A	See Note 2

[1] Adequate per prior reviews.
[2] Adequate information in NDA.

B. Other Documents: *IND, RLD, or sister applications*

Document	Application Number	Description
IND	119982	Development of golodirsen (SRP-4053) for treatment of DMD.
NDA	206488	Sarepta's approved NDA for the corresponding exon-51 skipping PMO, eteplirsen.
NDA	211970	Sarepta's approved NDA for the corresponding exon-53 skipping PMO, golodirsen.

2. CONSULTS

ONDP requested that the Office of Testing and Research (OTR) perform a product quality investigation of particle formation in casimersen injection on 1/11/2021. The applicant has agreed to cooperate with the OTR studies by supplying samples and analytical procedure when requested. The ongoing OTR investigation does not impact on approvability of the NDA.

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EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The OPQ review team has completed its evaluation of NDA 213026 for AMONDYS 45™ (casimersen injection). As detailed in the Product Quality review and Integrated Manufacturing Assessment, the review team identified one outstanding product quality concern, i.e., formation of visible particles in the product under long-term storage conditions, that are characterized by the applicant as inherent to the chemical and physical properties of casimersen. The presence of visible particles in a product intended for intravenous (IV) administration would normally preclude an approval recommendation for the application. However, the Division of Neurology 1 (DN1) clinical team has previously determined that: a) the clinical benefits of casimersen in the proposed patient population outweigh the risks associated with particulate matter; and b) use of a 0.2 µm in-line filter mitigates the risk.[1, 2] Therefore, OPQ recommends **APPROVAL** of the application. The approval recommendation is subject to post-marketing requirements (PMRs) as delineated below. Product Quality PMRs are deemed necessary because the applicant has not fully characterized the mechanism of particle formation and factors that could promote particle formation, or conclusively established that corrective actions to prevent particle formation are not feasible.

PMR 4005-8

We note a recent change in the analytical method for particulate matter characterization from USP <788> Microscopy (Method 2) to USP <788> Light Obscuration (Method 1) for release and stability testing. Submit interim particulate matter stability data using the revised analytical method (i.e., Method 1) as soon as the data are available per the proposed schedule outlined in the table entitled “Table 1: Estimated Timing for Casimersen Stability Data Using USP <788> Method 1” in the document entitled “qual-info-amend.pdf” in Section 1.11.1 of the amendment submitted on October 06, 2020.

Final Protocol Submission:	05/2021
Study/Trial Completion:	10/2023
Final Report Submission:	12/2023

[1] May 15, 2020, memorandum filed to IND 118086 (use of casimersen injection to promote formation of dystrophin in patients with mutations in the *DMD* gene that are amenable exon-skipping at exon 45) https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80564327&showAsPdf=true

[2] Instructions to use an in-line filter were added to labeling of Exondys 51 (eteplirsen injection) and Vyondys 53 (golodirsen injection) after post-approval reports of similar particulate matter under NDA (b) (4) /S-20 (5/29/2020) and NDA 211970/S-01 (8/19/2020), respectively.

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PMR 4005-9

The freeze/thaw and in-use stability data provided in the original submission used USP <788> Microscopy (Method 2) for particulate matter characterization. Repeat both studies using the USP <788> Light Obscuration (Method 1). These repeat studies should be performed using one batch of to-be-marketed (TBM) drug product manufactured at the commercial site.

Final Protocol Submission:	03/2021
Study/Trial Completion:	08/2021
Final Report Submission:	10/2021

PMR 4005-10

Per the document entitled "qual-info.pdf" in the amendment submitted on September 14, 2020, (b) (4) Independently perform these (b) (4) studies using casimersen drug product as well.

Final Protocol Submission:	05/2021
Study/Trial Completion:	12/2023
Final Report Submission:	03/2024

PMR 4005-11

Per the submission, the leachable study was performed using Lot 94EY-DT01 after 54 months of storage in the inverted position at 5 ± 3 °C. Repeat the leachable study using one batch of to-be-marketed (TBM) drug product manufactured at the commercial site during stability, where the data is collected at multiple stability time-points per the testing frequency recommended in ICH Q1A(R2).

Final Protocol Submission:	05/2021
Study/Trial Completion:	12/2024
Final Report Submission:	03/2025

Based on stability data provided, a (b) (4)-month retest date for the drug substance when stored at (b) (4)°C is granted. The assigned expiration dating period for the drug product is 24 months when stored refrigerated (5°C ± 3°C) in the commercial packaging.

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II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Sarepta Therapeutics proposes use of casimersen, a synthetic oligonucleotide analog, to treat Duchenne muscular dystrophy (DMD). DMD, a rare recessive X-linked form of muscular dystrophy, results in progressive muscle weakness and loss of muscle mass, loss of movement, and ultimately death. The disease is caused by mutations in *DMD*, the gene encoding dystrophin, a sarcolemma protein critical to the structural stability of myofibers in skeletal and cardiac muscle. Dystrophin mutations induce a shift in the open reading frame of the dystrophin transcript, leading to the absence of functional dystrophin protein.

The proposed product, AMONDYS 45 (casimersen injection) 50 mg/mL, is a sterile, isotonic, phosphate-buffered solution for intravenous infusion. Casimersen is a phosphorodiamidate morpholino oligomer (PMO) designed to target the pre-mRNA transcripts of the dystrophin gene so that exon 45 is excluded, or skipped, from the mature, spliced mRNA. Thus, casimersen is intended to restore the open reading frame for patients with *DMD* mutations amenable to exon 45 skipping and induce production of an internally deleted, functional dystrophin protein. Casimersen is the third PMO developed by the applicant for treatment of DMD. The previous products, Exondys 51 (eteplirsen injection) and Vyondys 53, are specific to *DMD* mutations amenable to exon 51 and exon 53 skipping, respectively.

Proposed indication including intended patient population	Treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 45 skipping.
Duration of treatment	Chronic, weekly infusions
Maximum daily dose	30 mg/kg
Alternative methods of administration	None

B. Quality Assessment Overview

Drug Substance: **Adequate**

Casimersen is a charge-neutral phosphorodiamidate morpholine oligomer (PMO) that selectively binds to exon 45 of dystrophin pre-mRNA. Casimersen contains 22 linked morpholino subunits that each contain one of the heterocyclic bases found in DNA (A, C, G, and T) and a hydrophilic triethylene glycol derived moiety (EG3 Tail) at the 5'-end.

The casimersen drug substance is manufactured using (b) (4) The regulatory starting

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materials are adequately justified and are acceptable based on ICH Q11. The manufacturing process is adequately described. Critical process parameters and in-process controls are in place to ensure the resulting drug substance is of acceptable quality. No ICH Q3C Class 1 solvents or toxic elements are used during the manufacture.

The applicant provides adequate characterization data for the drug substance, including MALDI-TOF MS, NMR spectroscopy, TGA, DSC (b) (4) The drug substance is hygroscopic and freely soluble in water and phosphate-buffered saline with a pH (b) (4). Casimersen is a (b) (4) The potential organic impurities have been evaluated and information on the structures, origins, fates, and control strategies for these impurities are provided. Process impurities are categorized (b) (4) This categorization of impurities is acceptable given the complexities of characterizing (b) (4) impurities and difficulties in resolving these impurities (b) (4)

The specification is sufficient to control the identity, purity, strength, and quality of the drug substance. Clinical, nonclinical, and registration batch analyses are provided and are within specifications.

The drug substance is packaged (b) (4) and is stored at (b) (4)°C. Based on the provided stability data under long-term and accelerated storage conditions, the proposed drug substance retest period, (b) (4) **months when stored at (b) (4)°C**, can be granted.

Drug Product: **Adequate with PMRs**

The proposed drug product contains100 mg casimersen in 2 mL (50 mg/mL) of a sterile, isotonic, phosphate-buffered saline (PBS) solution (pH 7.5). The drug product is filled into a glass vial with an elastomeric stopper and should be diluted into sterile 0.9% sodium chloride, USP prior to intravenous administration.

The proposed to-be-marketed (TBM) formulation contains excipients (b) (4) all excipients are of USP/NF grade and within IIG limits. Per the applicant, casimersen, is amphiphilic in nature and has the potential to adsorb to hydrophobic interfaces and subsequently forms subvisible particles and visible particles like proteins. The applicant has proposed an in-line 0.2 µm dosing filter to be used during administration; adequate instructions has been included on the label. The applicant has performed the in-use stability study to demonstrate that the drug product remains stable during preparation and administration using the IV bag system. An in-use compatibility study was also performed to demonstrate the compatibility of three commonly available 0.2 µm in-line filters together with the ancillary components. The light

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obscuration data showed that the particulates in the diluted drug product are reduced when filtered with an in-line filter set up. Overall control strategy, that included 100% visual inspection for visible particles during manufacturing, “no visible particles” specification at release, and instruction to use 0.2 µm in-line filter during infusion administration appears to mitigate the risk associated with API-related subvisible and visible particles in the product. However, the particulate matter test was previously performed under USP <788> and Ph. Eur 2.9.19 Method 2 (Microscopic Particle Count Test) during clinical development and stability testing. The data provided by the applicant indicate that the currently proposed test (i.e., Method 1) is more sensitive in detecting particulate matter. Per the applicant, USP <788> Method 1 has been implemented for casimersen release and stability testing in September 2020; therefore, only limited stability data is currently available using this method. In the absence of formal stability data, the particle growth rate over time cannot be determined at this time. Also freeze-thaw and in-use stability studies were performed using Method 2 and should be repeated using Method 1. Therefore, concerns remain about the safety of API-related particles in a product intended for intravenous administration over the shelf-life of the product. The applicant will perform the required studies to address these safety concerns under PMRs 4005-8, 4005-9, and 4005-10.

The applicant has provided 24, 18, and 12 months of long-term data for one registration batch each, along with 6 months of accelerated stability data for all three registration batches. The applicant has also provided up to 36 months of long-term supportive stability data. The registration stability batches were also used in the clinical studies. The applicant has also provided data for freeze thaw stability, photo stability, and extractable/leachable assessment. The submitted data supports the proposed shelf-life of 24 months with PMRs. Note that the leachable study was performed using a single batch after 54 months of storage in the inverted position at 5°C ± 3 °C, which is not sufficient to gain understanding about the release kinetics and any potential leachables degradation over time. The applicant will include leachable testing in the post-approval stability protocol for one commercial drug product batch under PMR 4005-11.

In addition to the PMRs discussed above, the Office of Testing and Research (OTR) has been asked to investigate the particulate matter observed in casimersen injection vials. The goal of these studies is to understand the mechanism of particle formation, and fully characterize the composition and physicochemical properties of the particles. The applicant has agreed to cooperate with this investigation by providing drug substance and drug product samples for analysis, and current analytical procedures when requested by the OTR.

Labeling: **Adequate**

The information in the proposed package insert and container labels is adequate from a product quality perspective.

Manufacturing: **Adequate**

The manufacturing process for casimersen injection consists of: (b) (4)

The applicant has established appropriate process parameters and in-process controls to ensure that casimersen injection conforms to all critical quality attributes, including freedom from visible particles at lot release. However, it was noted that the applicant is investigating (b) (4) A post-marketing commitment (PMC) to provide the results (b) (4) was recommended.[3]

All facilities involved in manufacture or testing of casimersen drug substance or Amondys 45™ (casimersen injection) are currently acceptable. Facility status should be verified prior to final action.

Microbiology: **Adequate**

Casimersen injection is (b) (4) In-process tests (b) (4), are adequately validated. The applicant provided an acceptable description and validation of hold times (b) (4) Procedures for (b) (4) vials, stoppers, and process equipment are adequately described and validated.

The finished product specification includes appropriate analytical procedures for bacterial endotoxin testing (BET), sterility testing, and container closure integrity testing (CCIT). BET and sterility testing will be performed at product release. BET and CCIT will be performed on stability. All analytical procedure are validated and deemed adequate for quality control.

[3] Following discussions within the Office of New Drug Products ONDP), and with the clinical division, the applicant agreed to a post-marketing requirement (PMR 4005-10) to perform a (b) (4) study for casimersen injection.

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Methods Verification:

The OTR performed method verification for the following drug product test methods.

Identification, Monoisotopic Mass by LC/MS (ESI): The method was deemed acceptable for quality control and regulatory purposes, with a modification recommended. In OTR's verification, the retention time of the SRP-4045 (casimersen) peak is at (b) (4) This recommendation has been communicated to the applicant.

Assay, Purity and Impurities by Ion-Pairing HPLC and Impurity (b) (4) by SCX Chromatography: Both methods were deemed acceptable for quality control and regulatory purposes.

Environmental:

The applicant submitted a claim for categorical exclusion under 21 CFR §25.31(b). Approval of the NDA would increase use of the active moiety; however, the projected maximum usage of the active ingredient is (b) (4) kg per year. Per Dr. Raanan (Ron) Bloom of the Environment Assessment Team, this usage is considered to be at a de minimus level; meaning, a very low risk of significant environmental impact is anticipated from use of this pharmaceutical. The applicant provides a statement of no extraordinary circumstances. Thus, a formal environmental assessment review is not needed and the claim for categorical exclusion is accepted.

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C. Final Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Comments**
Sterility	Formulation, container closure, process parameters, scale, equipment, site	**High**	The applicant established adequate procedures equipment, container closure, and drug product sterilization. Appropriate in-process and finished product controls.	**Adequate**	
Endotoxins/Pyrogens	Formulation, container closure, process parameters, scale, equipment, site	**Moderate**	Adequate procedures for container closure (b) (4) BET at release and on stability.	**Adequate**	
Assay/stability	Formulation, raw materials, container closure, process parameters, scale, equipment, site	**Low**	Analytical procedures are appropriate and validated. Key methods were verified by OTR. Assessed in long-term stability studies.	**Adequate**	
Fill volume/delivered volume	Formulation, container closure, process parameters, scale, equipment, site	**Low**	In process (b) (4) and release testing,	**Adequate**	
Osmolality	Formulation, container closure, process parameters, scale, equipment, site	**Low**	Phosphate buffered saline vehicle is isotonic. Osmolality of product is in acceptable range (260 to 320 mmol/kg)	**Adequate**	

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From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Comments**
pH (high)	Formulation, raw materials, container closure, process parameters, scale, equipment, site	**Low**	Product pH (b) (4) is acceptable to ensure product stability. No evidence of glass delamination due to high pH.	**Adequate**	
Particulate matter	Formulation, raw materials, container closure, process parameters, scale, equipment, site	**Moderate**	Formation of particulate matter on storage is observed in casimersen injection and related PMOs. Current mitigation strategy, i.e., use of an in-line filter during administration is acceptable to ensure availability of casimersen to the intended patients. Additional studies to characterize mechanism of particle formation and evaluate feasibility of measures to prevent particle formation will be required post-approval.	**Adequate with PMRs**	Post-approval studies under PMRs to be managed by ONDP.
Leachable/extractables	Formulation, raw materials, container closure, process parameters, scale, equipment, site	**Low**	Compatibility with manufacturing equipment demonstrated. Potential container closure extractables were not present at quantifiable levels in stability samples.	**Adequate**	
Appearance	Formulation, raw materials, container closure, process parameters, scale, equipment, site	**Low**	Visual inspection at release for absence of particles. See comments above regarding particulate matter formation on storage	**Adequate**	

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D. List of Deficiencies for Complete Response

Not applicable; however, the PMRs listed in Section I should be conveyed in the final action letter.

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.
CMC Lead for Neurology Products
Office of New Drug Products

2/16/2021

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/s/

MARTHA R HEIMANN
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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

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	TRADENAME	Add final Trandname.throughout the document.
Established name(s)	(casimersen) injection	Acceptable
Route(s) of administration	for intravenous use	Acceptable
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Injection: 100 mg/2 mL in a single-dose vial	Acceptable
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	Acceptable

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1.2 FULL PRESCRIBING INFORMATION
1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

2.2 Dosing Information

The recommended dose of TRADENAME is 30 milligrams per kilogram administered once weekly as a 35 to 60-minute intravenous (IV) infusion via an in-line 0.2 micron filter.

If a dose of TRADENAME is missed, it may be administered as soon as possible after the scheduled dose.

2.3 Preparation Instructions

TRADENAME is supplied in single-dose vials as a preservative-free concentrated solution that requires dilution prior to administration. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Use aseptic technique.

a. Calculate the total dose of TRADENAME to be administered based on the patient's weight and the recommended dose of 30 milligrams per kilogram. Determine the volume of TRADENAME needed and the correct number of vials to supply the full calculated dose.

b. Allow the vials to warm to room temperature. Mix each vial by gently inverting 2 or 3 times. Do not shake.

c. Visually inspect each vial of TRADENAME. The solution is a clear to slightly opalescent, colorless liquid, and may contain trace amounts of small, white to off-white amorphous articles. Do not use if the solution in the vials is cloudy, discolored or contains extraneous particulate matter other than trace amounts of small, white to off-white amorphous particles.

d. With a syringe fitted with a 21 gauge or smaller bore non-coring needle, withdraw the calculated volume of TRADENAME from the appropriate number of vials. To avoid dulling the needle and fragmenting the stoppers, replace the needle periodically during preparation.

e. Dilute the withdrawn TRADENAME in 0.9% Sodium Chloride Injection, USP, to make a total volume of 100-150 mL. Gently invert 2 to 3 times to mix. Do not shake. Visually inspect the diluted solution. Do not use if the solution is cloudy, discolored or contains extraneous particulate matter other than trace amounts of small, white to off-white amorphous particles.

f. Administer the diluted solution via an in-line 0.2 micron filter.

g. TRADENAME contains no preservatives and should be administered immediately after dilution. Complete infusion of diluted TRADENAME within 4 hours of dilution. If immediate use is not possible the diluted product may be stored for up to 24 hours at 2 °C to 8 °C (36 °F to 46 °F). Do not freeze. Discard unused TRADENAME.

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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)	See above excerpt	Acceptable

3 DOSAGE FORMS AND STRENGTHS

TRADENAME is a clear to slightly opalescent, colorless liquid and may contain trace amounts of small, white to off-white amorphous particles and is available as:

- Injection: 100 mg/2 mL (50 mg/ mL) solution in a single-dose vial

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Reference ID: 4747772

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Injection	Acceptable
Strength(s) in metric system	100 mg/2 mL (50 mg/ mL)	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	clear to slightly opalescent, colorless liquid and may contain trace amounts of small, white to off-white amorphous particles	Acceptable
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 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 vial	Acceptable

1.2.3 Section 11 (DESCRIPTION)

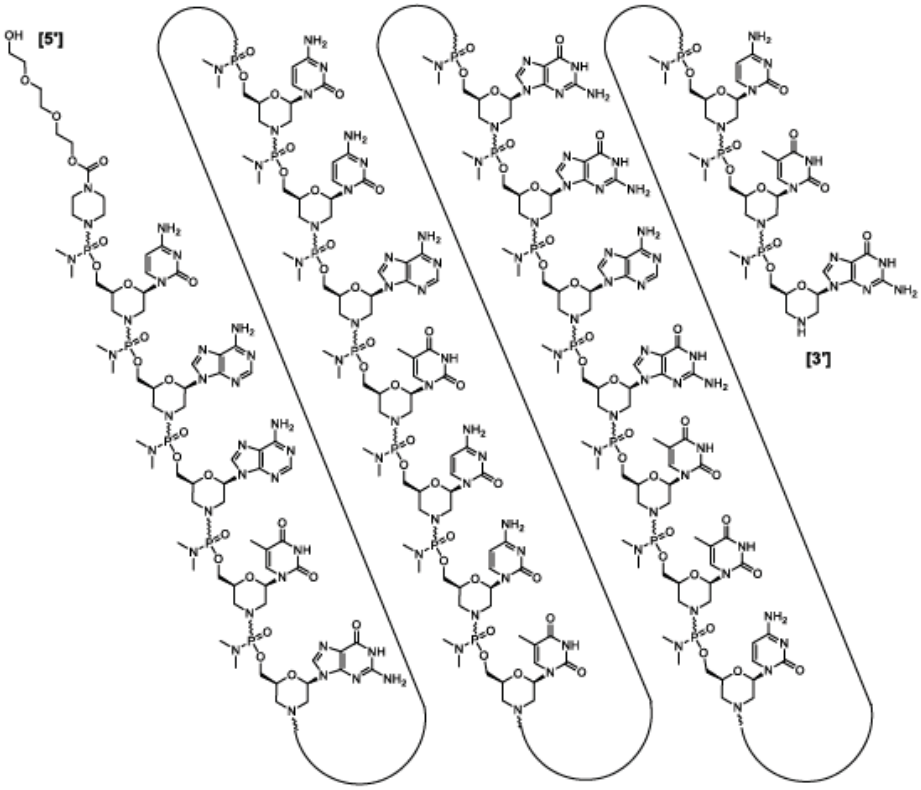
11 DESCRIPTION

TRADENAME (casimersen) injection is a sterile, aqueous, preservative-free, concentrated solution for dilution prior to intravenous administration. TRADENAME is a clear to slightly opalescent, colorless liquid and may contain trace amounts of small, white to off-white amorphous particles. TRADENAME is supplied in single-dose vials containing 100 mg casimersen (50 mg/mL). TRADENAME is formulated as an isotonic phosphate buffered saline solution with an osmolality of 260 to 320 mOSM and a pH of 7.5. Each milliliter of TRADENAME contains: 50 mg casimersen; 0.2 mg potassium chloride; 0.2 mg potassium phosphate monobasic; 8 mg sodium chloride; and 1.14 mg sodium phosphate dibasic, anhydrous, in water for injection. The product may contain hydrochloric acid or sodium hydroxide to adjust pH.

Casimersen is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) subclass. PMOs are synthetic molecules in which the five-membered ribofuranosyl rings found in natural DNA and RNA are replaced by a six-membered morpholino ring. Each morpholino ring is linked through an uncharged phosphorodiamidate moiety rather than the

negatively charged phosphate linkage that is present in natural DNA and RNA. Each phosphorodiamidate morpholino subunit contains one of the heterocyclic bases found in DNA (adenine, cytosine, guanine, or thymine). Casimersen contains 22 linked subunits. The sequence of bases from the 5' end to 3' end is CAATGCCATCCTGGAGTTCCTG. The molecular formula of casimersen is $C_{268}H_{424}N_{124}O_{95}P_{22}$ and the molecular weight is 7584.5 daltons.

The structure of casimersen is:



Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	TRADENAME (casimersen) injection	Add final tradename throughout the document
Dosage form(s) and route(s) of administration	concentrated solution for dilution prior to intravenous administration	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	50 mg casimersen; 0.2 mg potassium chloride; 0.2 mg potassium phosphate monobasic; 8 mg sodium chloride; and 1.14 mg sodium phosphate dibasic, anhydrous, in water for injection. The product may contain hydrochloric acid or sodium hydroxide to adjust pH.	Acceptable
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.	See above	Acceptable
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	a sterile, aqueous, preservative-free	Acceptable

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Pharmacological/ therapeutic class	Casimersen is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) subclass	Acceptable
Chemical name, structural formula, molecular weight	See above excerpt	Acceptable
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	TRADENAME is formulated as an isotonic phosphate buffered saline solution with an osmolality of 260 to 320 mOSM and a pH of 7.5.	Acceptable

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	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	No promotional statement found.	Acceptable

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Reference ID: 4747772

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Injection	Acceptable
Strength(s) in metric system	100 mg/2 mL (50 mg/mL)	Acceptable
Available units (e.g., bottles of 100 tablets)	Single-dose vials	Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	The solution is a clear to slightly opalescent, colorless liquid, and may contain trace amounts of small, white to off-white amorphous particles.	Acceptable
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	Acceptable

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 until ready for use to protect from light.	Acceptable
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.	Store TRADENAME at 2 °C to 8 °C (36 °F to 46 °F).	Acceptable
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	N/A	

1.2.5 Other Sections of Labeling

Reference ID: 4747772

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)

Manufactured for:
Sarepta Therapeutics, Inc.
Cambridge, MA 02142 USA

Sarepta and Sarepta Therapeutics are trademarks of Sarepta Therapeutics, Inc. registered in the U.S. Patent and Trademark Office and may be registered in various other jurisdictions.
TRADENAME and TRADENAME logo are trademarks of Sarepta Therapeutics, Inc.

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	See excerpt above	Acceptable

2.0 PATIENT LABELING

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 Container Label

(Copy/paste or refer to a representative example of a proposed container)

Reference ID: 4747772

(b) (4)

3.2 Carton Labeling

(Copy/paste or refer to a representative example of a proposed carton labeling)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Included	Replace TRADENAME 45 with the final tradename
Dosage strength	100 mg/2mL	Acceptable
Route of administration	Injection; for intravenous use after dilution	Acceptable
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	
Net contents (e.g. tablet count)	N/A	
"Rx only" displayed on the principal display	Included	Acceptable
NDC number	Included	Acceptable
Lot number and expiration date	Included	Acceptable
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Included	Acceptable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Single dose	Acceptable
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Included	Acceptable

Reference ID: 4747772

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Included	Acceptable
Medication Guide (if applicable)	N/A	
No text on Ferrule and Cap overseal		Acceptable
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	
And others, if space is available	None	

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

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

ITEMS FOR ADDITIONAL ASSESSMENT

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor Name and Date: Renishkumar Delvadia

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

Reference ID: 4747772

Renishkumar Delvadia

Digitally signed by Renishkumar Delvadia
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Julia Pinto

Digitally signed by Julia Pinto
Date: 2/10/2021 02:46:59PM
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FDA U.S. FOOD & DRUG ADMINISTRATION

MICROBIOLOGY

Product Information	Indicated for the Treatment of Duchenne muscular dystrophy (DMD) in (b) (4) patients with a confirmed mutation of the DMD gene that is amenable to exon 45 skipping.
NDA Number	213026
Assessment Cycle Number	1
Drug Product Name / Strength	Casimersen, 50 mg/ mL
Route of Administration	IV Infusion
Applicant Name	Sarepta Therapeutics, Inc.
Manufacturing Site	(b) (4)
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Theme:

☒ N/A	☐ (b) (4) 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: *view justification statements found at:* **Justification Statements**

N/A

Assessment Summary:

- This review covers sterility assurance and microbiological quality of the drug product.
- The product is (b) (4) No deficiencies were identified.

List Submissions Being Assessed (table):

Submit	Received	Review Request	Assigned to Reviewer
6/25/2020	6/25/2020	N/A	07/06/2020
08/04/2020	08/04/2020	N/A	N/A
9/25/2020	9/25/2020	N/A	9/28/2020

Highlight Key Issues from Last Cycle and Their Resolution: NA

Concise Description of Outstanding Issues: None

Supporting Documents:

• DMF (b) (4) and product quality microbiology review D (b) (4) M01R01.docx dated 01/30/2020 (adequate) for facility description and floor plans

• NDA 21060/ Supp 10 and product quality microbiology review N21060S10r1.doc dated 12/14/2012 (adequate) for initial validation studies (b) (4) for stoppers and equipment load

• NDA 209296/ Supp (b) (4) nd product quality microbiology review N209296S (b) (4) .pdf dated 03/27/2019 (adequate) for revalidation studies for the above (b) (4) for stoppers and equipment load as well as (b) (4) validation of vials

• NDA 213994 and product quality microbiology review N213994MR01.doc dated 04/07/2020 (adequate) for environmental monitoring program, (b) (4) requalification runs covering worst-case stopper and equipment loads and (b) (4) validation of vials

• NDA 211970 and product quality microbiology review N211970MR01.pdf dated 05/17/2019 (adequate) for revalidation studies (b) (4) for stopper load

• DMF (b) (4) and product quality microbiology review D (b) (4) M33R01.doc dated 02/03/2017 (adequate) for stopper (b) (4)

An information request (IR) was conveyed on 09/18/2020 and a response was received from the applicant on 09/25/2020. The response to the IR is covered in this review.

Select Number of Approved Comparability Protocols: 00

S DRUG SUBSTANCE

Assessment: The drug substance (b) (4) Therefore, microbiology review will not be conducted for drug substance.

P DRUG PRODUCT

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Description of drug product – The drug product is a sterile isotonic solution of 50 mg casimersen per mL of phosphate-buffered solution (pH 7.5) that is filled in a single-use 2-mL glass vial for intravenous administration. The solution is a clear to slightly opalescent, colorless liquid, and may contain white to off-white particles.

- **Drug product composition -**
  (3.2.P.1, Description and composition)

Table 2. Composition of the Dosage Form

Component	Reference to Standards	Quantity (mg/mL)	Function
Casimersen drug substance[1]	3.2.S.4.1	50	Active ingredient
Sodium chloride	USP, Ph. Eur.	8.0	(b) (4)
Potassium chloride	USP, Ph. Eur.	0.2	
Potassium phosphate monobasic	NF, Ph. Eur.	0.2	
Sodium phosphate dibasic, anhydrous	USP, Ph. Eur.	1.14	
Sodium hydroxide[2]	NF, Ph. Eur.	q.s.	
Hydrochloric acid[2]	NF, Ph. Eur.	q.s.	
Water for Injection[3]	USP, Ph. Eur.	q.s.	

[1] (b) (4)
[2] q.s. = quantity sufficient for pH adjustment.
[3] q.s. = quantity sufficient to achieve final volume

Exhibit Batch size: (b) (4) L (approximately (b) (4) vials)
Maximum Proposed Commercial Batch size: (b) (4) L (approximately (b) (4) vials).

- **Description of container closure system**
  (3.2.P.7.)

Component	Description	Manufacturer
Vial	2-mL, clear, USP (b) (4)	(b) (4)
Stopper	13-mm, grey (b) (4) rubber stopper (USP/Ph. Eur. (b) (4) elastomeric closure), (b) (4)	
Seal	13mm Aluminum shell with flip-off cap overseal	

Assessment: An adequate description of the drug product composition and container closure system was provided.

Adequate

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

(b) (4)

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(b) (4)

[redacted]

Assessment: The applicant provided an acceptable description of the container closure integrity test (CCIT) and adequate data following CCIT validation studies.

Adequate

Antimicrobial Effectiveness Testing

(3.2.P.2.)

The subject drug product is a single dose; antimicrobial effectiveness testing is not required.

Assessment:

Adequate

P.3 MANUFACTURE

P.3.1 MANUFACTURERS

(b) (4)

[redacted]

P.7 CONTAINER CLOSURE

Summary Table of the Container Closure System Proposed – See P.1

P.8 STABILITY

P.8.1 STABILITY SUMMARY AND CONCLUSION

See P.8.2.

P.8.2 POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT

(3.2.P.8.2)

The long-term stability testing schedule at 5°C±3°C (inverted position) in the post-approval protocol is as follows:

Stability Test	Time (Months)						
	0	6	9	12	18	24	36
Sterility	X						
BET	X			X		X	X
CCIT*	X			X		X	X

*Dye ingress method used

Proposed Expiry: 24 months

Post Approval Stability Commitment: Post approval, the applicant commits to continuing and completing the long-term stability studies to confirm the shelf life according to ICH Q1A. Additionally, the applicant commits to placing one lot of drug

product on stability (for 36 months at the long-term storage condition 5 ± 3 °C) annually for each year in which at least one lot of that drug product is produced.

Assessment:

Adequate

P.8.3 STABILITY DATA

Stability studies were provided for Casimersen injection. All the batches passed microbiological testing as summarized in Table below:
The stability study will be continued for the remaining period as per the stability study protocol provided.

Test	Accelerated 25°C /60% RH	Long-term 5°C
Sterility	(b) (4)	
BET		
CCIT		

Assessment: Adequate stability results for sterility testing for product quality microbiology were provided to support the proposed shelf life of 24 months.

Adequate

R REGIONAL INFORMATION

Executed Batch Records
Executed lot numbers: SE0003
The batch record confirms that validated (b) (4) manufacturing processes were used for the manufacture of the exhibit batch.

Assessment:

Adequate

Reference ID: 4747772

Comparability Protocols
NA

2. ASSESSMENT OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Prescribing Information
(Package Insert)
(1.14.1.3)

Dosage and Administration:
The recommended dose is 30 mg/kg body weight once/ week to be administered as an intravenous (IV) infusion over 35 to 60 minutes via an in-line 0.2 micron filter.

Reconstituted/Further Diluted Drug Product:
The drug product is prepared by calculating the dose based on the patient's weight and diluted in 0.9% sodium chloride to a total volume of 100-150 mL. The diluted product must be used within 4 hours of dilution or within 24 hours if under refrigeration.

Assessment:

Adequate

MICROBIOLOGY LIST OF DEFICIENCIES: None

Primary Microbiology Assessor Name and Date:
Aditi Das, Ph.D., 10/26/2020

Secondary Assessor Name and Date:
Neal Sweeney, Ph.D., 10/26/2020

Reference ID: 4747772

Aditi Das

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Neal Sweeney

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/s/

MARTHA R HEIMANN
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