CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211970Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approve

NDA 211970
Review 1

Drug Name/Dosage Form	Golodirsen Injection
Strength	100 mg/2 mL (50 mg/mL)
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Sarepta Therapeutics
US agent, if applicable	N/A

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Rohit Tiwari	Su Tran
Drug Product	Rao Kambhampati	Wendy Wilson-Lee
Process	Erin Kim	Nallaperumal Chidambaram
Microbiology	Jennifer Patro	Jesse Wells
Facility	Erin Kim	Ying Zhang
Biopharmaceutics	N/A	--
Regulatory Business Process Manager	Dahlia Walters	--
Application Technical Lead	Martha Heimann	--
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental	N/A	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SD-001, CMC module for rolling submission	08/27/2018	All
SD-002, Response to IR	10/29/2018	Microbiology
SD-003, Response to IR	11/08/2018	Drug substance
SD-004, Final NDA module	12/19/2018	Product, labeling
SD-006, Response to IR	01/04/2019	Process
SD-007, Response to IR	01/08/2019	Microbiology
SD-015, Labeling, package insert draft	02/02/2019	Labeling
SD-016, Stability update	03/06/2019	Product
SD-022, Labeling, carton/container draft	04/15/2019	Labeling

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	V		(b) (4)	Adequate [1]	10/03/2012	
	III			N/A [1]	--	
	V			Adequate [1]	02/03/2017	
	III			N/A [1]	--	

[1] Adequate information in application or no changes to information since previous adequate reviews.

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.

2. CONSULTS

None

Executive Summary

I. Recommendations and Conclusion on Approvability

The OPQ review team recommends **APPROVAL** of NDA 211970 for Golodirsen Injection for intravenous infusion. A (b) (4) month retest date is granted for the drug substance when stored (b) (4), and a 24-month expiration dating period is granted for the drug product when stored refrigerated.

There are no recommended post-marketing commitments.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	Treatment of Duchenne muscular dystrophy (DMD) in pediatric and adult patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 53 skipping.
Duration of Treatment	Chronic
Maximum Daily Dose	30 mg per kg body weight once *weekly*
Alternative Methods of Administration	None

Sarepta Therapeutics proposes use of golodirsen, 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. Golodirsen is a phosphorodiamidate morpholino oligomer (PMO) designed to target the pre-mRNA transcripts of the dystrophin gene so that exon 53 is excluded, or skipped, from the mature, spliced mRNA. Thus, golodirsen is intended to restore the open reading frame for patients with *DMD* mutations amenable to exon 53 skipping and induce production of an internally deleted, functional dystrophin protein. Golodirsen is the second PMO developed by the applicant for treatment of DMD. The first, Exondys 51 (eteplirsen injection), is specific to *DMD* mutations amenable to exon 51 skipping.

B. Quality Assessment Overview

Factors critical to the OPQ evaluation of the submission were the adequacy of the synthesis, purification, characterization, and control strategy for the drug substance, manufacture and

control of the product, and sterility assurance to support intravenous administration. The applicant has adequately addressed concerns identified during the review.

Drug Substance

The drug substance, golodirsen, contains a sequence of 25 linked (dimethylamino)-phosphorodiamidate morpholino subunits. It is functionalized with a hydrophilic triethylene glycol-derived "tail" at the 5′ end that enhances aqueous solubility. Each subunit of golodirsen contains one of the heterocyclic bases found in DNA, adenine (A), cytosine (C), guanine (G), and thymine (T or m^5U). Golodirsen differs from natural ribose-based oligonucleotides, and synthetic phosphorothioate oligonucleotides, in that: a) the heterocyclic bases of golodirsen are attached to a morpholino group, not a ribose unit, and b) the linkages between subunits are neutral, not negatively charged. The absolute stereochemistry of the morpholino residue (1′*R*, 4′*S*) is controlled by (b) (4) .

Golodirsen is manufactured using (b) (4) . The designated starting materials, manufacturing process, critical process parameters and critical in process controls for the (b) (4) are adequately described and justified. (b) (4)

The golodirsen drug substance is adequately characterized by standard analytical methods (UV, HRMS, Molecular Sequencing, HPLC, ^1H, ^{13}C and ^{31}P NMR) that are used for oligonucleotide-based therapeutics. The regulatory specification for golodirsen drug substance includes appropriate tests and acceptance criteria for critical quality attributes (CQAs) that include appearance, identification (monotopic mass and sequencing), assay, purity, and related substances (IP-HPLC), residual solvents, water content, residue on ignition, pH (1% solution), bacterial endotoxins and microbial limits. Process impurities are adequately characterized and their limits in the drug substance specification are qualified in nonclinical studies.

The drug substance is stored in (b) (4) The available stability data support a (b) (4) month retest date for drug substance stored under these conditions.

Drug Product

Golodirsen injection is a sterile, preservative-free, clear to slightly opalescent solution for intravenous infusion. It is supplied as single-dose vials containing 100 mg golodirsen per 2 mL phosphate-buffered saline in a 2-mL, (b) (4) glass vial. The proposed dose of golodirsen is 30 mg/kg administered by iv infusion once per week. The product must be diluted in saline prior to use.

The commercial manufacturing process for golodirsen injection consists of standard unit processes. (b) (4) The manufacturing process and in-process controls are adequately described and deemed suitable for commercial production.

The release specification for golodirsen injection includes tests for drug product CQAs such as appearance, identity (molecular weight), assay, purity, specified impurities, elemental impurities, pH, osmolality, sterility, bacterial endotoxins, and particulate matter. The observed impurities are derived from the drug substance; there are no formulation specific degradation products. Non-compendial analytical procedures used for product release are similar to those used for the drug substance. The primary differences are related to sample preparation. The analytical procedures are adequately validated and suitable for their intended use.

Methods Verification

Verification of drug product IP-HPLC UV methods (identity, assay, and impurities), SCX Chromatography ((b) (4) impurity), LC/MS (ESI) method (identification, monoisotopic mass) was performed by the Division of Pharmaceutical Analysis (DPA). The methods were found acceptable for quality control and regulatory purposes, with a recommended modification to the LC/MS (ESI) method. For the LC/MS (ESI) method, the analyst noted that in DPA's results, the retention time of the SRP-4053 peak is at 4.29 min (UV) and 4.41 min (MS TIC), which differs from the from the applicant's results (8.8 min). Therefore, DPA recommends that in the applicant's method the Scan Time "(b) (4) " be revised to read "0-2.5 minutes and 19-20 minutes to Waste" to assure the SRP-4053 peak will not be inadvertently discarded in the waste. The recommendation will be conveyed to the applicant; however, it does not affect approvability of the application.

Facilities

All facilities that will be involved in commercial manufacture and testing of golodirsen and golodirsen injection are currently acceptable.

C. Special Product Quality Labeling Recommendations

The product should be stored at 2°C – 8°C and labeled "Do Not Freeze."
Once diluted, the product should not be stored for more than 4 hours at room temperature or 24 hours refrigerated.

D. Final Risk Assessment for Golodirsen Injection

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Sterility		**H**	Use of validated [redacted] (b) (4) for sterilization.	Adequate	
Endotoxin, pyrogen		**M**	Control for endotoxins in bulk drug substance and final product. Validated depyrogenation procedures for packaging components	Adequate	
Assay, stability	• Formulation • Container closure • Raw materials • Process parameters • Scale • Equipment • Site	**L**	Refrigerated storage provides for acceptable shelf	Adequate	
Fill volume/delivered volume		**L**	[redacted] (b) (4) Tested at release	Adequate	
Osmolality		**L**	Release test, target within physiological range. Product diluted with normal saline prior to infusion.	Adequate	
pH (high)		**L**	Phosphate buffer, target pH 7.5	Adequate	
Particulate matter		**M**	Compendial release and stability test. Delamination low risk due to neutral pH and refrigerated storage.	Adequate	
Leachable/Extractables		**L**	Compatibility with manufacturing equipment demonstrated. Potential container closure extractables were not present at quantifiable levels in stability samples.	Adequate	
Appearance		**L**	Visual inspection	Adequate	

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LABELING

Review of NDA 211970

R Regional Information

1.14 Labeling

Immediate Container (vial) Label:

(b) (4)

Reviewer's Assessment: Adequate.

The *vial label complies with all the regulatory requirements from a CMC perspective.*

Carton Label:

(b) (4)

[redacted]

Reviewer's Assessment: Adequate.

Carton label comply with all the regulatory requirements from a CMC perspective.

List of Deficiencies: None

Primary Labeling Reviewer Name and Date: Rao V. Kambhampati, Ph.D. 5/17/19

Secondary Reviewer Name and Date:

Rao Kambhampati

Digitally signed by Rao Kambhampati
Date: 5/17/2019 01:06:04PM
GUID: 508da72000029fd06e8c9283b7414189

Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 5/17/2019 01:11:00PM
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MICROBIOLOGY

Product Background:

NDA/ANDA: 211970

Drug Product Name / Strength: Golodirsen for Injection

Route of Administration: injection

Applicant Name: Sarepta Therapeutics

Manufacturing Site: (b) (4)

Method of Sterilization: (b) (4)

Review Recommendation: **Adequate**

Theme (ANDA only): Choose an item.

Justification (ANDA only): Choose an item.

Review Summary: This is a sterile solution filled into single-use vials. The product is (b) (4). The product contact equipment sterilized via (b) (4) and container closure system is (b) (4) (b) (4).

List Submissions Being Reviewed: 08/27/2018; 10/29/18 IR response; 12/16/2018 final submission (labeling); 01/18/2019 IR response

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: This is a rolling submission with product quality data submitted on 08/27/2018. An IR was submitted on 10/17/2018 after the completion of the filing review. This review will cover both the original submission and the IR response.

Concise Description Outstanding Issues Remaining: N/A

Supporting Documents: Review of building and facility DMF (b) (4) in (b) (4) 2011feb25 a1.doc on October 3, 2012.

Jesse Wells

Digitally signed by Jesse Wells
Date: 1/25/2019 07:12:58AM
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Jennifer Patro

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Martha Heimann

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