CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 206-488/S-006

Trade Name: Exondys 51

Generic Name: eteplirsen injection

Sponsor: Sarepta Therapeutics, Inc.

Approval Date: February 8, 2018

Indications: For the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 206-488/S-006

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Approvable Letter	
Labeling	**X**
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	**X**
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Other Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 206-488/S-006

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206488/S-006

SUPPLEMENT APPROVAL

Sarepta Therapeutics, Inc.
Attention: Shamim Ruff, MSc.
Sr. Vice President, Regulatory Affairs and Quality
215 First Street, Suite 415
Cambridge, MA 02142

Dear Ms. Ruff:

Please refer to your Supplemental New Drug Application (sNDA) dated August 10, 2017, received August 10, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Exondys 51 (eteplirsen) injection, 50 mg/mL.

This Prior Approval supplemental new drug application provides for revisions to the prescribing information related to hypersensitivity reactions. The revisions include the addition of a new subsection 5.1 (Hypersensitivity Reactions) of the Warnings and Precautions section and the addition of corresponding information and a cross-reference in subsection 2.3 (Dosage and Administration; Administration Instructions). The revisions also include the addition of information about hypersensitivity reactions to a newly created Section 17 (Patient Counseling Information).

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Fannie Choy, Regulatory Project Manager, at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Alice Hughes, M.D.
Deputy Director for Safety
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALICE HUGHES
02/08/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 206-488/S-006

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EXONDYS 51® safely and effectively. See full prescribing information for EXONDYS 51.

EXONDYS 51 (eteplirsen) injection, for intravenous use
Initial U.S. Approval: 2016

RECENT MAJOR CHANGES

Dosage and Administration, Administration Instructions (2.3)	2/2018
Warnings and Precautions, Hypersensitivity Reactions (5.1)	2/2018

INDICATIONS AND USAGE

EXONDYS 51 is an antisense oligonucleotide indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with EXONDYS 51 *[see Clinical Studies (14)]*. A clinical benefit of EXONDYS 51 has not been established. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials. (1)

DOSAGE AND ADMINISTRATION

- 30 milligrams per kilogram of body weight once weekly (2.1)
- Administer as an intravenous infusion over 35 to 60 minutes (2.1, 2.3)
- Dilution required prior to administration (2.2)

DOSAGE FORMS AND STRENGTHS

Injection:
- 100 mg/2 mL (50 mg/mL) in single-dose vial (3)
- 500 mg/10 mL (50 mg/mL) in single-dose vial (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions: Hypersensitivity reactions, including pyrexia, flushing, cough, dyspnea, bronchospasm, rash, urticaria, and hypotension, have occurred in patients treated with EXONDYS 51. If hypersensitivity reactions occur, institute appropriate medical treatment and consider slowing the infusion or interrupting the EXONDYS 51 therapy. (2.3, 5.1)

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥35% and higher than placebo) were balance disorder and vomiting (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sarepta Therapeutics, Inc. at 1-888-SAREPTA (1-888-727-3782) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 02/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EXONDYS 51 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with EXONDYS 51 *[see Clinical Studies (14)]*. A clinical benefit of EXONDYS 51 has not been established. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of EXONDYS 51 is 30 milligrams per kilogram administered once weekly as a 35 to 60 minute intravenous infusion.

If a dose of EXONDYS 51 is missed, it may be administered as soon as possible after the scheduled time.

2.2 Preparation Instructions

EXONDYS 51 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 EXONDYS 51 to be administered based on the patient's weight and the recommended dose of 30 milligrams per kilogram. Determine the volume of EXONDYS 51 needed and the correct number of vials to supply the full calculated dose.

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

c. Visually inspect each vial of EXONDYS 51. EXONDYS 51 is a clear, colorless solution that may have some opalescence. Do not use if the solution in the vials is discolored or particulate matter is present.

d. With a syringe fitted with a 21-gauge or smaller non-coring needle, withdraw the calculated volume of EXONDYS 51 from the appropriate number of vials.

e. Dilute the withdrawn EXONDYS 51 in 0.9% Sodium Chloride Injection, USP, to make a total volume of 100-150 mL. Visually inspect the diluted solution for particulates.

f. EXONDYS 51 contains no preservatives and should be administered immediately after dilution. Complete infusion of diluted EXONDYS 51 solution within 4 hours of dilution. If immediate use is not possible, the diluted solution may be stored for up to

24 hours at 2ºC to 8ºC (36ºF to 46ºF). Do not freeze. Discard unused EXONDYS 51.

2.3 Administration Instructions

Application of a topical anesthetic cream to the infusion site prior to administration of EXONDYS 51 may be considered.

EXONDYS 51 is administered via intravenous infusion. Flush the intravenous access line with 0.9% Sodium Chloride Injection, USP, prior to and after infusion.

Infuse the diluted EXONDYS 51 solution over 35 to 60 minutes. Do not mix other medications with EXONDYS 51 or infuse other medications concomitantly via the same intravenous access line.

If a hypersensitivity reaction occurs, consider slowing the infusion or interrupting the EXONDYS 51 therapy *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

3 DOSAGE FORMS AND STRENGTHS

EXONDYS 51 is a clear and colorless solution that may have some opalescence, and is available as follows:

- Injection: 100 mg/2 mL (50 mg/mL) solution in a single-dose vial
- Injection: 500 mg/10 mL (50 mg/mL) solution in a single-dose vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions, including rash and urticaria, pyrexia, flushing, cough, dyspnea, bronchospasm, and hypotension, have occurred in patients who were treated with EXONDYS 51. If a hypersensitivity reaction occurs, institute appropriate medical treatment and consider slowing the infusion or interrupting the EXONDYS 51 therapy *[see Dosage and Administration (2.3)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the EXONDYS 51 clinical development program, 107 patients received at least one intravenous dose of EXONDYS 51, ranging between 0.5 mg/kg (0.017 times the recommended dosage) and 50 mg/kg (1.7 times the recommended dosage). All patients were male and had genetically confirmed Duchenne muscular dystrophy. Age at study entry was 4 to 19 years. Most (89%) patients were Caucasian.

EXONDYS 51 was studied in a double-blind, placebo-controlled study for 24 weeks (Study 1), followed by an open label extension (Study 2). In Study 1, 12 patients were randomized to receive weekly intravenous infusions of EXONDYS 51 (n=8) or placebo (n=4) for 24 weeks. All 12 patients continued in Study 2 and received open-label EXONDYS 51 weekly for up to 208 weeks.

In Study 1, 4 patients received placebo, 4 patients received EXONDYS 51 30 mg/kg, and 4 patients received EXONDYS 51 50 mg/kg (1.7 times the recommended dosage). In Study 2, 6 patients received EXONDYS 51 30 mg/kg/week and 6 patients received EXONDYS 51 50 mg/kg/week *[see Clinical Studies (14)]*.

Adverse reactions that occurred in 2 or more patients who received EXONDYS 51 and were more frequent than in the placebo group in Study 1 are presented in Table 1 (the 30 and 50 mg/kg groups are pooled). Because of the small numbers of patients, these represent crude frequencies that may not reflect the frequencies observed in practice. The 50 mg/kg once weekly dosing regimen of EXONDYS 51 is not recommended *[see Dosage and Administration (2.1)]*.

The most common adverse reactions were balance disorder and vomiting.

Table 1. Adverse Reactions in DMD Patients Treated with 30 or 50 mg/kg/week[1] EXONDYS 51 with Incidence at Least 25% More than Placebo (Study 1)

Adverse Reactions	EXONDYS 51 (N=8) %	Placebo (N=4) %
Balance disorder	38	0
Vomiting	38	0
Contact dermatitis	25	0

[1] 50 mg/kg/week = 1.7 times the recommended dosage

In the 88 patients who received ≥30 mg/kg/week of EXONDYS 51 for up to 208 weeks in clinical studies, the following events were reported in ≥10% of patients and occurred more frequently than on the same dose in Study 1: vomiting, contusion, excoriation, arthralgia, rash, catheter site pain, and upper respiratory tract infection.

Hypersensitivity reactions have occurred in patients treated with EXONDYS 51 *[see Warnings and Precautions (5.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no human or animal data available to assess the use of EXONDYS 51 during pregnancy. In the U.S. general population, major birth defects occur in 2 to 4% and miscarriage occurs in 15 to 20% of clinically recognized pregnancies.

8.2 Lactation

Risk Summary

There are no human or animal data to assess the effect of EXONDYS 51 on milk production, the presence of eteplirsen in milk, or the effects of EXONDYS 51 on the breastfed infant.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EXONDYS 51 and any potential adverse effects on the breastfed infant from EXONDYS 51 or from the underlying maternal condition.

8.4 Pediatric Use

EXONDYS 51 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping, including pediatric patients *[see Clinical Studies (14)]*.

Intravenous administration of eteplirsen (0, 100, 300, or 900 mg/kg) to juvenile male rats once weekly for 10 weeks beginning on postnatal day 14 resulted in renal tubular necrosis at the highest dose tested and decreased bone densitometry parameters (mineral density, mineral content, area) at all doses. The kidney findings were associated with clinical pathology changes (increased serum urea nitrogen and creatinine, decreased urine creatinine clearance). No effects were observed on the male reproductive system, neurobehavioral development, or immune function. An overall no-effect dose was not identified. Plasma eteplirsen exposure (AUC) at the lowest dose tested (100 mg/kg) was similar to that in humans at the recommended human dose (30 mg/kg).

8.5 Geriatric Use

DMD is largely a disease of children and young adults; therefore, there is no geriatric experience with EXONDYS 51.

8.6 Patients with Renal or Hepatic Impairment

EXONDYS 51 has not been studied in patients with renal or hepatic impairment.

10 OVERDOSAGE

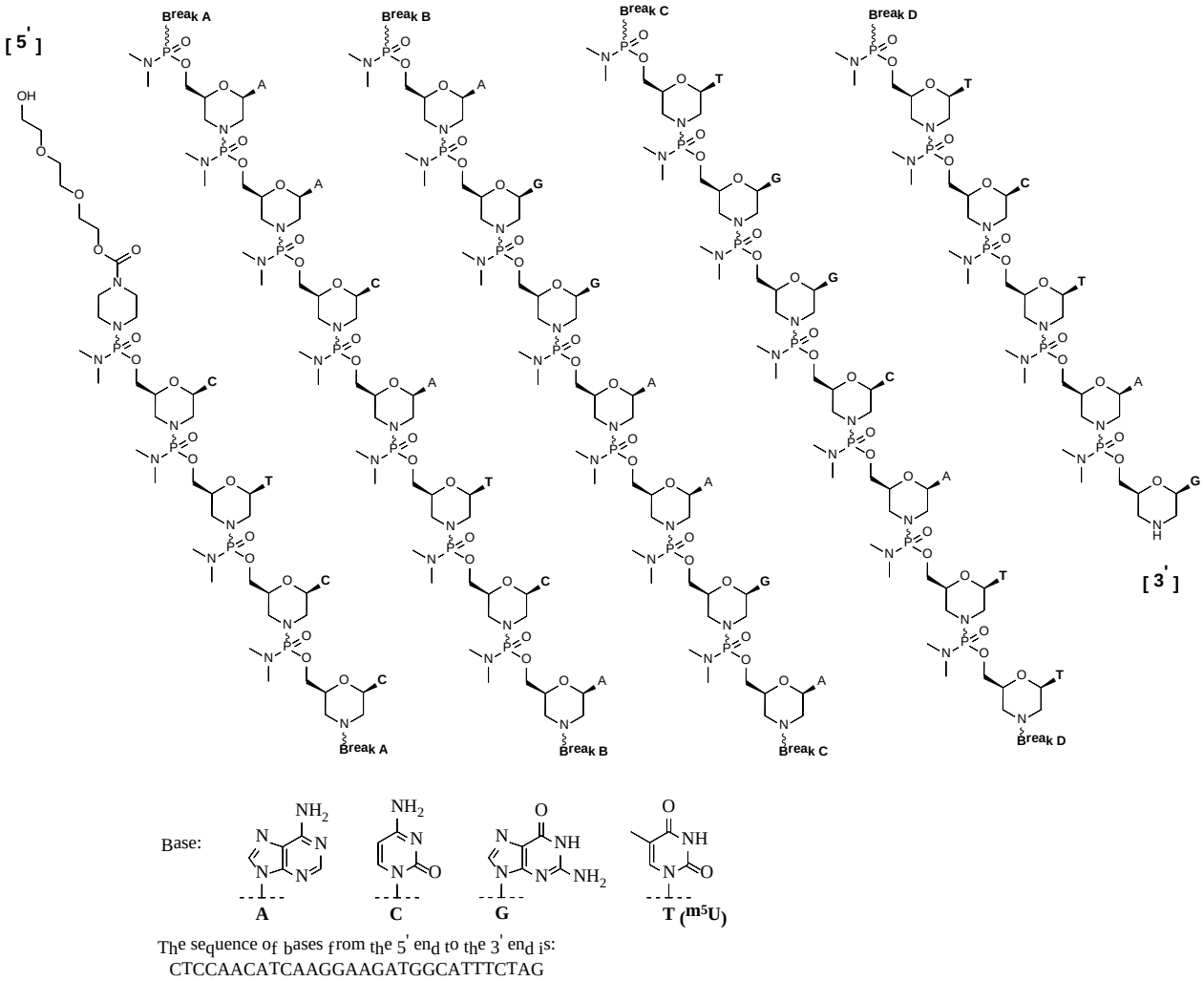
There is no experience with overdose of EXONDYS 51.

11 DESCRIPTION

EXONDYS 51 (eteplirsen) injection is a sterile, aqueous, preservative-free, concentrated solution for dilution prior to intravenous administration. EXONDYS 51 is clear and colorless, and may have some opalescence. EXONDYS 51 is supplied in single dose vials containing 100 mg or 500 mg eteplirsen (50 mg/mL). EXONDYS 51 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 EXONDYS 51 contains 50 mg eteplirsen; 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.

Eteplirsen 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). Eteplirsen contains 30 linked subunits. The molecular formula of eteplirsen is $C_{364}H_{569}N_{177}O_{122}P_{30}$ and the molecular weight is 10305.7 daltons.

The structure and base sequence of eteplirsen are:



The sequence of bases from the 5' end to the 3' end is:
CTCCAACATCAAGGAAGATGGCATTTCTAG

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Eteplirsen is designed to bind to exon 51 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 51 skipping. Exon skipping is intended to allow for production of an internally truncated dystrophin protein, which was evaluated in Study 2 and Study 3 [*see Clinical Studies (14)*].

12.2 Pharmacodynamics

All EXONDYS 51-treated patients evaluated (n=36) were found to produce messenger ribonucleic acid (mRNA) for a truncated dystrophin protein by reverse transcription polymerase chain reaction.

In Study 2, the average dystrophin protein level in muscle tissue after 180 weeks of treatment with EXONDYS 51 was 0.93% of normal (i.e., 0.93% of the dystrophin level in healthy subjects). Because of insufficient information on dystrophin protein levels before treatment with

EXONDYS 51 in Study 1, it is not possible to estimate dystrophin production in response to EXONDYS 51 in Study 1.

In Study 3, the average dystrophin protein level was 0.16% of normal before treatment, and 0.44% of normal after 48 weeks of treatment with EXONDYS 51 *[see Clinical Studies (14)]*. The median increase in truncated dystrophin in Study 3 was 0.1% *[see Clinical Studies (14)]*.

12.3 Pharmacokinetics

Following single or multiple intravenous infusions of EXONDYS 51 in male pediatric DMD patients, plasma concentration-time profiles of eteplirsen were generally similar and showed multi-phasic decline. The majority of drug elimination occurred within 24 hours. Approximate dose-proportionality and linearity in PK properties were observed following multiple-dose studies (0.5 mg/kg/week [0.017 times the recommended dosage] to 50 mg/kg/week [1.7 times the recommended dosage]). There was no significant drug accumulation following weekly dosing across this dose range. The inter-subject variability for eteplirsen C_{max} and AUC range from 20 to 55%.

Following single or multiple intravenous infusions of EXONDYS 51, the peak plasma concentrations (C_{max}) of eteplirsen occurred near the end of infusion (i.e., 1.1 to 1.2 hours across a dose range of 0.5 mg/kg/week to 50 mg/kg/week).

Distribution

In vitro investigation suggested that plasma protein binding of eteplirsen in human ranges between 6 to 17%. The mean apparent volume of distribution (Vss) of eteplirsen was 600 mL/kg following weekly intravenous infusion of EXONDYS 51 at 30 mg/kg.

Twenty-four hours after the end of the infusion, mean concentrations of eteplirsen were 0.07% of C_{max}. Accumulation of eteplirsen during once weekly dosing has not been observed.

Elimination

The total clearance of eteplirsen was 339 mL/hr/kg following 12 weeks of therapy with 30 mg/kg/week.

Metabolism

Eteplirsen did not appear to be metabolized by hepatic microsomes of any species tested, including humans.

Excretion

Renal clearance of eteplirsen accounts for approximately two-thirds of the administered dose within 24 hours of intravenous administration. Elimination half-life ($t_{1/2}$) of eteplirsen was 3 to 4 hours.

Specific Populations

Age:

The pharmacokinetics of eteplirsen have been evaluated in male pediatric DMD patients. There is no experience with the use of EXONDYS 51 in patients 65 years of age or older.

Sex:

Sex effects have not been evaluated; EXONDYS 51 has not been studied in female patients.

Race:

Potential impact of race is not known because 89% of the patients in studies were Caucasians.

Renal or Hepatic Impairment:

EXONDYS 51 has not been studied in patients with renal or hepatic impairment.

Drug Interaction Studies

In vitro data showed that eteplirsen did not significantly inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5. Eteplirsen did not induce CYP2B6 or CYP3A4, and induction of CYP1A2 was substantially less than the prototypical inducer, omeprazole. Eteplirsen was not a substrate nor did it have any major inhibitory potential for any of the key human transporters tested (OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, P-gp, BCRP, MRP2 and BSEP). Based on *in vitro* data on plasma protein binding, CYP or drug transporter interactions, and microsomal metabolism, eteplirsen is expected to have a low potential for drug-drug interactions in humans.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies have not been conducted with eteplirsen.

Mutagenesis

Eteplirsen was negative in *in vitro* (bacterial reverse mutation and chromosomal aberration in CHO cells) and *in vivo* (mouse bone marrow micronucleus) assays.

Impairment of Fertility

Fertility studies in animals were not conducted with eteplirsen. No effects on the male reproductive system were observed following intravenous administration of eteplirsen (0, 5, 40, or 320 mg/kg) to male monkeys once weekly for 39 weeks. Plasma eteplirsen exposure (AUC) in monkeys at the highest dose tested was 20 times that in humans at recommended human dose (30 mg/kg).

14 CLINICAL STUDIES

EXONDYS 51 was evaluated in three clinical studies in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

In Study 1, patients were randomized to receive weekly infusions of EXONDYS 51 (30 mg/kg, n=4); EXONDYS 51 (50 mg/kg, n=4), or placebo (n=4) for 24 weeks. The primary endpoint was dystrophin production; a clinical outcome measure, the 6-minute walk test (6MWT), was also assessed. The 6MWT measures the distance that a patient can walk on a flat, hard surface in a period of 6 minutes. Patients had a mean age of 9.4 years, a mean 6-minute walk distance

(6MWD) at baseline of 363 meters, and were on a stable dose of corticosteroids for at least 6 months. There was no significant difference in change in 6MWD between patients treated with EXONDYS 51 and those treated with placebo.

All 12 patients who participated in Study 1 continued treatment with open-label EXONDYS 51 weekly for an additional 4 years in Study 2. The 4 patients who had been randomized to placebo were re-randomized 1:1 to EXONDYS 51 30 or 50 mg/kg/week such that there were 6 patients on each dose. Patients who participated in Study 2 were compared to an external control group. The primary clinical efficacy outcome measure was the 6MWT. Eleven patients in Study 2 had a muscle biopsy after 180 weeks of treatment with EXONDYS 51, which was analyzed for dystrophin protein level by Western blot. Study 2 failed to provide evidence of a clinical benefit of EXONDYS 51 compared to the external control group. The average dystrophin protein level after 180 weeks of treatment with EXONDYS 51 was 0.93% of the dystrophin level in healthy subjects. Because of insufficient information on dystrophin protein levels before treatment with EXONDYS 51 in Study 1, it is not possible to estimate dystrophin production in response to EXONDYS 51 in Study 1.

In Study 3, 13 patients were treated with open-label EXONDYS 51 (30 mg/kg) weekly for 48 weeks and had a muscle biopsy at baseline and after 48 weeks of treatment. Patients had a mean age of 8.9 years and were on a stable dose of corticosteroids for at least 6 months. Dystrophin levels in muscle tissue were assessed by Western blot. In the 12 patients with evaluable results, the pre-treatment dystrophin level was 0.16% ± 0.12% (mean ± standard deviation) of the dystrophin level in a healthy subject and 0.44% ± 0.43% after 48 weeks of treatment with EXONDYS 51 ($p < 0.05$). The median increase after 48 weeks was 0.1%.

Individual patient dystrophin levels from Study 3 are shown in Table 2.

Table 2. Western Blot Results: EXONDYS 51-Treated (Week 48) vs Pre-treatment Baseline (% Normal Dystrophin) (Study 301)

Patient Number	Baseline % normal dystrophin	Week 48 % normal dystrophin	Change from Baseline % normal dystrophin
1	0.13	0.26	0.13
2	0.35	0.36	0.01
3	0.06	0.37	0.31
4	0.04	0.10	0.06
5	0.17	1.02	0.85
6	0.37	0.30	-0.07
7	0.17	0.42	0.25

8	0.24	1.57	1.33
9	0.11	0.12	0.01
10	0.05	0.47	0.43
11	0.02	0.09	0.07
12	0.18	0.21	0.03
Mean	0.16	0.44	0.28; p=0.008

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

EXONDYS 51 injection is supplied in single-dose vials. The solution is clear and colorless, and may have some opalescence.

- Single-dose vials containing 100 mg/2 mL (50 mg/mL) eteplirsen NDC 60923-363-02
- Single-dose vials containing 500 mg/10 mL (50 mg/mL) eteplirsen NDC 60923-284-10

16.2 Storage and Handling

Store EXONDYS 51 at 2°C to 8°C (36°F to 46°F). Do not freeze. Protect from light and store EXONDYS 51 in the original carton until ready for use.

17 PATIENT COUNSELING INFORMATION

Hypersensitivity Reactions

Advise patients and/or caregivers that symptoms of hypersensitivity, including bronchospasm and hypotension, can occur with EXONDYS 51. Instruct them to seek immediate medical care should they experience signs and symptoms of hypersensitivity *[see Warnings and Precautions (5.1)]*.

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 206-488/S-006

MEDICAL REVIEW(S)

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Neurology Products
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Clinical Review

NDA / Supporting Document Number:	206488 / S-006 (NDA Sequence Number 0099)
Drug Name (Generic):	Exondys 51 (eteplirsen)
Applicant:	Sarepta
Indication:	Duchenne Muscular Dystrophy
Type of Submission:	Prior Approval Labeling Supplement
Date of Submission:	August 10, 2017
Date of Review:	February 8, 2018
Reviewer:	Christopher D. Breder, MD PhD
Project Manager:	Fannie Choy

I. Background

A. Regulatory

Exondys 51 (eteplirsen) was approved using the accelerated approval pathway on September 19, 2016. For the final labeling at the time of approval, adverse reactions (ARs) in the table of common ARs were based on having an incidence of 25% more than placebo[1] in the placebo-controlled study '201'. ARs from openlabel studies were included if the incidence was greater than 10% of the 88 subjects in this population. Symptoms of hypersensitivity with an incidence below 10% in the open-label group were also included because of their clinical importance.

On August 10, 2017, the applicant submitted a prior approval labeling supplement that proposed to revise the Adverse Reactions section of the EXONDYS 51 Full Prescribing Information (PI) to include language describing hypersensitivity events, as below (strikethrough is used to indicate related existing language that the applicant proposed to delete).

Section 6.1 Clinical Trials Experience

(b) (4)

[1] N=8 active and 4 placebo in this study.

~~There have been reports of transient erythema, facial flushing, and elevated temperature occurring on days of EXONDYS 51 infusion.~~

The criteria used by applicant to determine which ARs to include in the labeling are discussed in my critique in Section II.B of this review.

On October 19, 2017 (NDA Sequence Number 0111) the applicant subsequently proposed further revised labeling language for hypersensitivity. Note the strikethrough has been removed in the sentence beginning with "…There have been reports…"

Section 6.1 Clinical Trials Experience

There have been reports of transient erythema, facial flushing, and elevated temperature occurring on days of EXONDYS 51 infusion.

(b) (4)

An information request (IR) was sent to the applicant on November 6, 2017, that requested detailed information related to the proposed language.

A follow-up IR was sent January 2, 2018, that requested further information as well as electronic datasets containing information on postmarketing events.

II. Clinical Review

A. Materials reviewed

In addition to the currently approved labeling and the two versions of the proposed labeling, the following documents were also reviewed:

1. Summary Documents

    a) Module 5.3.5.3 - Document 0115(130 rec'd 12/8/17) - Integrated Summary of Safety - Tables and Listings - PAS

    b) Module 1.11.3 - Document 0115(130 rec'd 12/8/17) - Safety Assessment - Hypersensitivity Analysis

    c) Module 1.11.3 - Document 0115(130 rec'd 12/8/17) Summary of Exondys 51 Post Marketing Cases Retrieved by Hypersensitivity SMQ as of 31Oct2017

2. Electronic Datasets

    a) Module 5.3.5.3 - Document 0115(130 rec'd 12/8/17) - ADSL, Subject level; ADEX, exposure; ADAE, adverse event

    b) Module 5.3.5.3 – Document 0123(136 rec'd 1/05/2018) – POSTMARK (postmarketing cases demographic and AE information)

B. Summary and Critique of Applicant's Submission

The applicant's discussion in this supplement is divided into data derived from patients in clinical trials and from postmarketing spontaneous reports.

Applicant's Assessment of Trial Data

According to the applicant's document entitled "Hypersensitivity analysis," the following criteria were used in its analysis of hypersensitivity from trial data for this supplement[2]:

As of the 12 May 2017, cut-off date, 200 subjects received at least one dose of eteplirsen. Of those, 160 were DMD patients exposed to once weekly, intravenous (IV) infusions, 33 non- DMD subjects who were exposed to a single IV infusion and 7 DMD patients who received a single intramuscular injection of eteplirsen.

Data from DMD patients who received multiple IV infusions (N=160) are the primary dataset for the clinical trial analysis. Data regarding non-DMD subjects (N=33) who received a single IV infusion are presented separately for completeness.

Adverse events (AEs) were reviewed and assigned as [infusion-related reaction] *IRRs[3] based on meeting both of following*

Inclusion criteria:

[2] Materials substantially extracted verbatim in the applicant's wording are presented in italics.
[3] All events described by the applicant will be termed IRRs to denote the criterion used to select these events unless the applicant explicitly uses the term 'events'.

- *AE occurred on the day of and after the start of infusion. For those events where infusion start time was not reported the default was to assign the AE as an IRR, and*
- *AE resolution was on the same day as the infusion except for rash AEs, which could have any duration.*

*An AE that met the above IRR inclusion criteria was **not** included if any of the following exclusion criteria were met:*

- *AE was an infusion site, application site, or other local site-type AE,*
- *AE had a clear alternate etiology that could be ascertained based on the reported event (e.g., itchy rash on both calves from braces),*
- *AE had a low probability of being consistent with an IRR due to the nature of the event (e.g., muscle weakness resulting in a fall).*

Table 1 Clinical Trial IRRs in > 1 DMD Patient (Data Cut-off 12-May-2017)

Preferred Term	Patients [1] N=160 n (%)	Number of IRRs
All patient with at least 1 IRR	**73 (46)**	**160**
Rash[2]	22 (14)	34
Headache	22 (14)	31
Vomiting [3]	11 (7)	13
Nausea	9 (6)	9
Pyrexia [4]	6 (4)	6
Dizziness	5 (3)	5
Chest pain [5]	5 (3)	5
Muscle spasms	5 (3)	5
Diarrhoea	5 (3)	5
Flushing	4 (3)	4
Oropharyngeal pain	4 (3)	4
Arrhythmia [6]	3 (2)	3
Cough	3 (2)	5
Abdominal pain [7]	3 (2)	4
Pain in extremity	2 (1)	2
Back pain	2 (1)	2
Dyspepsia	2 (1)	2
Fatigue	2 (1)	2

[1] A single patient could have experienced more than one IRR; therefore, may be included in more than one PT.

[2] Rash includes Preferred Terms (PT) and (# IRRs): Rash (9), Urticaria (4), Erythema (4), Rash generalized (3), Rash papular (2), Erythema of eyelid (2), Papule (2), Rash pruritic (1), Drug eruption (1), Cold urticaria (1), Pruritus (1), Dermatitis contact (1), Skin hyperpigmentation (1), Acne (1), Petechia (1)

[3] Vomiting includes PTs: Vomiting (12), Post-tussive vomiting (1)

[4] Pyrexia includes PTs: Pyrexia (5), Body temperature increased (1), Infusion related reaction (1, reported term was "Temperature elevation up to 37.9 degrees after infusion)

[5] Chest pain include PTs: Chest pain (2), Chest discomfort (2), Non-cardiac chest pain (1)

[6] Arrhythmia includes PTs: Arrhythmia (1), Sinus tachycardia (1), Ventricular tachycardia (1)

[7] Abdominal pain includes PT: Abdominal pain upper (3), Abdominal pain (1)

Source: hypersens-analysis.pdf, pp6-7

All IRRs were considered mild except in 7 patients who experienced 10 IRRs of moderate severity that included[4] Cough, Vomiting, Diarrhea, Rash generalized, Headache, Non-cardiac chest pain, Urticaria (2 patients), Ventricular tachycardia, and Vomiting.

The following table summarizes the 6 cases of reported IRRs (based on the applicant's criteria) where treatment was discontinued.

Table 2 IRRs Leading to Treatment Discontinuation

Patient ID	Age	IRR Preferred Term	Severity	IRR Onset from Infusion Start (hours:minutes)	IRR Duration[1]	Dose No. at time of IRR	Total No. Doses Received
301-A1-230-004[2]	7	Urticaria	Moderate	01:14	1 day	88	109
301-A1-207-002[3]	11	Rash generalized	Moderate	05:17	3 days	62	79
301-A1-230-001	9	Cough	Moderate	00:05	1 day	64	127
301-A1-217-004	10	Dyspnoea	Mild	00:02	1 day	1	84
201/202-6	10	Cold urticaria	Mild	00:44	1 day	4	284
201/202-9	9	Erythema	Mild	00:02	1 day	85	305

[1] IRR Onset from Infusion Start of "1 day" refers to patients with no infusion start time and IRR start on day of infusion.
[2] IRR was also reported as an SAE
[3] Patient 301-A1-207-002 experienced an IRR of Rash generalized, which occurred 5hrs 17 mins after the infusion, but is included in this table given that the Investigator reported the Action Taken as "Drug interrupted" because the next scheduled infusion was not administered due to this event.

Source: hypersens-analysis.pdf, p9

One event was assessed by the Investigator as serious. This event is described below:

Patient 301-A1-230-004
Patient was a 7-year-old male (30 mg/kg) who received an eteplirsen infusion on Study Day 611: Study Week 88 (07 December 2016). Approximately 15-20 minutes after the infusion, the patient experienced generalized itching. Approximately 20-30 minutes after the start of the infusion the patient's condition worsened and he developed flushing welts, papules, redness, and swelling from head to trunk. Blood pressure was 122/105 mmHg, heart rate was 128 beats per minute, respiratory rate was 26 breaths per minute and temperature was 99.8◦ F. The patient was treated with methylprednisolone and diphenhydramine. After 20 minutes vital signs normalized. The urticaria resolved approximately 1 hour after treatment. On 20 December 2016, the patient underwent skin testing with eteplirsen, which was negative. On 20 December 2016 and 03 January 2017, the patient was pre-treated with Solu-Medrol and Benadryl prior to each of the eteplirsen infusions. No adverse IRRs were reported during the infusions. On 18 January 2017, the patient received eteplirsen infusions with no pretreatment medication and no

[4] By convention MedDRA preferred terms (adverse events or reactions) will be written with the first letter of the first term capitalized. SMQ names will be written in italics also with the first letter of the first term capitalized.

adverse IRRs were reported. The patient continued eteplirsen infusions without pre-treatment medications and no adverse IRRs were reported during infusions. Investigation of the two lots used for the infusions that resulted in adverse IRRs did not reveal a product quality issue. The investigator assessed the event of Urticaria as moderate in severity and definitely related to eteplirsen.

Applicant's Assessment of Postmarketing Data

From the time of marketing approval on September 16, 2016, through October 31, 2017, there have been a total of 264 patients exposed to eteplirsen in the post-marketing setting. From this total, 183 (69%) patients did not participate in eteplirsen clinical trials and were therefore naïve to eteplirsen. As of the data cut-off of October 31, 2017, there have been a total of 83 (83/264, 31%) patients who have reported a total of 228 AEs in the post-marketing setting. Several of the patients have reported AEs on more than one occasion; therefore, there are 97 case reports for the 83 patients in the applicant's safety database.

The following table, copied from the application, summarizes the results of the AE analysis of IRRs based on the applicant's criteria, noted above.

Table 3 Post-marketing IRRs in > 1 Patient (Data through 31 October 2017)

Preferred Term	Patients N= 264 n (%)	Number of IRRs
All patient with at least 1 IRR	**17 (7)**	**49**
Flushing	6 (2)	6
Cough	4 (2)	4
Fatigue	4 (2)	4
Chest pain [2]	3 (1)	3
Bronchospasm	2 (1)	2
Dyspnoea	2 (1)	2
Cyanosis	2 (1)	2
Pyrexia	2 (1)	2
Malaise	2 (1)	2
Rash [2]	2 (1)	2
Emotional distress [3]	2 (1)	2

[2] Chest pain includes Preferred Terms (PTs) (# of IRRs): Chest discomfort (2), Chest pain (1).

[3] Rash includes PTs: Rash (1), Skin hyperpigmentation (1).

[4] Emotional distress includes PTs: Emotional distress and Irritability in the same patient (1), Anger and Bite in same patient (1: Bite Reported term "Started to bite")

Source: hypersens-analysis.pdf, p11

Of the 19 infusions with IRRs, 7 (37%) had the infusion either stopped and restarted, or slowed. Table 4 presents the action taken.

Table 4 Patients with IRRs and Action Taken with Infusion

Action Taken with Infusion	Number of infusions
Stopped/restarted or slowed	7
Stopped and restarted with gravity tubing	*2*
Infusion stopped and catheter flushed [1]	*3*
Infusion slowed	*2*
Other [2]	3
Not reported	5
None	4

[1] Infusions were stopped and catheters flushed with normal saline. One patient also received diphenhydramine after after flushing.
[2] "Other" includes treatment with Tylenol (1 patient), analgesics (1 patient).

Source: hypersens-analysis.pdf, p11

Two patients (Case ID: SRP-000041-2017 and SRP-00002-2017) experienced IRRs of Bronchospasm that were assessed by the manufacturer as SAEs and as unexpected according to the EXONDYS 51 Unites States Package Insert. The following provides a verbatim summary for each patient.

Case ID SRP-000041-2017

Preferred Terms: Bronchospasm (SAE), Cough, Chest pain, Chest discomfort

Patient was a 16 year-old male with DMD who previously participated in eteplirsen clinical trials and received therapy for 5 years. Patient's other medical history included hypothyroidism, and seasonal allergies. The patient had no prior history of bronchospasm. Concomitant medications were not reported. Patient received 5 prior infusions in the postmarketing setting without incident. Prior to the sixth infusion, the patient reported feeling well. Six minutes into the infusion the patient reported chest pain described as 8.5 out of 10 chest pressure and burning. The patient was transported to the emergency room (ER). While in transit the patient's father noted a cough that that patient did not have prior to the infusion. Chest x-ray was unremarkable, and showed the central port was properly positioned. The patient's infusion nurse also noted that she was able to obtain good blood return from the port. After 30 minutes in the ER the patient's chest pain persisted. Patient was treated with unspecified breathing treatments and sent home. At 19:30 hours on the same day the patient's chest pain had subsided to 7 out of 10. The patient went on to receive additional infusions without incident.

Case SRP-000067-2017

Preferred Terms: Bronchospasm (SAE), Cough, Chest discomfort, Dysphagia

Patient was a 12 year old male with DMD and a port placed for central venous access. The patient had no other significant medical history and concomitant medications were not reported. On the day of the patient's first infusion, and pre-infusion, vital signs noted a blood pressure (BP) of 106/64, heart rate (HR) 108, respiration rate (RR) 18, and temperature (T) 98.5. Five minutes after start of the infusion the patient experienced moderate bronchospasm.

The patient was also noted to have a cough, chest tightness, difficulty swallowing and was spitting clear mucous. After 10 minutes into the infusion BP was 116/63, HR 115, RR 18 and T 98.4. The infusion was stopped, the catheter was flushed with normal saline, and the patient was treated with diphenhydramine. The bronchospasm resolved after 25 minutes. The cough was also noted to have resolved. Vital signs at the time of

bronchospasm resolution were BP 104/62, HR 105, RR 18 and T 98.4. The following day the patient received the remaining infusion from the prior day without incident.

Medical Officer's Comments: The analysis that has been conducted by the applicant was potentially restrictive given the criteria (specified on page 3 of this review) for IRRs. Accordingly, I felt that an original, comprehensive, and systematic analysis may provide an additional and potentially more accurate perspective on the incidence of events that were hypersensitivity-related. This analysis is detailed in the next section.

C. Medical Reviewer Analysis

Methodology

Adverse events were analyzed by manual review of the datasets and by using the MedDRA-based Adverse Events Diagnostics (MAED) program to evaluate hypersensitivity-related events. However, within that domain, I did not restrict my analysis to the Standardized MedDRA Query (SMQ) for Hypersensitivity. Rather, a series of SMQs were used as screening tools to identify a more comprehensive listing of potentially hypersensitivity-related events. The following table provides a list of SMQs used in this analysis:

Table 5 List of SMQs to Identify Potential Hypersensitivity-Related Events

Level 1	Level 2
(1) Anaphylactic reaction	
(1) Drug reaction with eosinophilia and systemic symptoms syndrome	
(1) Hypersensitivity	
(1) Eosinophilic pneumonia	
(1) Shock	
(1) Shock	*(2) Shock-associated circulatory or cardiac conditions (excl torsade de pointes)*
(1) Shock	*(2) Toxic-septic shock conditions*
(1) Angioedema	
(1) Asthma/bronchospasm	
(1) Shock	*(2) Hypovolaemic shock conditions*
(1) Shock	*(2) Anaphylactic/anaphylactoid shock conditions*

Preferred terms identified by this search were evaluated for incidence for placebo-controlled data (Trials 201/202) in the case of trial data. I selected these data because they were the only intravenous, repeat-dosed, placebo-controlled data at the labeled dose strengths of 30 and 50 mg, i.e., identical to what the drug is labeled. For the postmarketing data, a single arm numerator analysis for the risk (exposed with condition/total exposed) was performed that generated the proportion of subjects who were 'SMQ-positive" and the 95% confidence bounds. This is in contrast to a placebo-controlled study where an odds or risk ratio can be calculated. For description of the results, a positive signal was considered if the lower bound of the 95% CI was ≥ 2. In the postmarketing analyses, all terms contributing to SMQ positive cases are reported.

Prior to analysis, preferred terms from the trial (Table 8) and postmarketing (Table 9) datasets were consolidated based on clinical similarities.

Since I was interested in events in the hypersensitivity domain, I do not report events I considered to be outside of that scope here (i.e., not identified by the SMQs listed in or relevant by my inspection of the adverse event datasets provided by the applicant). Unlike the applicant's analysis I did not limit the time frame of event to the day of and after infusion. Events in hypersensitivity reactions may often be delayed, particularly rashes and exanthema, which may follow a week or more after other symptoms [1, 2].

Results

Premarket Analysis

None of the SMQs (Table 5) used in the analysis demonstrated a significant imbalance of cases in the EXONDYS51 treatment arm. Table 6 provides the AE terms identified by the SMQs in the premarket AE database where the average incidence of the 30 and 50 mg treatment groups used in the 201/202 trials was greater than that of placebo. As with the applicant's analyses, these findings are limited by the small number of subject's in the placebo arm.

Table 6 Incidence of Subjects having AEs Identified by Hypersensitivity-Related AEs

AEDECOD	N Subjects w AE (30 mg/kg)	% Incidence (30mg)	N Subjects w AE (50 mg/kg)	% Incidence (50mg)	AVG AE Incidence	N Subjects w AE (Placebo)	% Incidence (PBO)
Papule	1	17	1	17	17	0	0
Rash	4	67	1	17	42	0	0
Urticaria	1	17	1	17	17	0	0

Postmarketing Analysis

SMQ analysis of the postmarketing database suggested a disproportionate number of AEs in the analysis of narrow SMQ Hypersensitivity terms (Table 11, 7.69%; 4.1-13.97)[5] . An algorithmic analysis[6] of the *SMQ Anaphylactic reaction* (Table 10) did not meet the prespecified rule proposed for analysis; however, the lower limit was 1.84% which was very close to being considered positive. Several SMQs were positive using a broad analysis (Table 12) including *SMQ Anaphylactic reaction, Drug reaction with eosinophilia, and systemic symptoms syndrome,* and *Hypersensitivity,* which had a lower 95% CI limit greater than 10%.

Terms identified by the SMQs are noted in Table 7 in order of their incidence.

[5] (Proportion; 95%CI bounds)
[6] Per the standard technique described in the *Introductory Guide for Standardised MedDRA Queries (SMQs) Version 16.0*, MSSO, McClean VA (2013), p.20, which an algorithmically positive event is defined by having either a narrow (essentially diagnostic) term from Category A OR a term from Category B - (Upper Airway/Respiratory) AND a term from Category C - (Angioedema/Urticaria/Pruritus/Flush) OR a term from Category D - (Cardiovascular/Hypotension) AND [a term from Category B - (Upper Airway/Respiratory) OR a term from Category C - (Angioedema/Urticaria/ Pruritus/Flush)].

Table 7 Terms identified by the SMQs in Postmarketing Data

AEDECODF	N Patients	Incidence (%) (N_{total}=117)
Pyrexia	11	9
Flushing	8	7
Cough	7	6
Dyspnoea	4	3
Rash	4	3
Chest discomfort	3	3
Infusion related reaction	3	3
Pneumonia	3	3
Respiratory failure	3	3
Alanine aminotransferase increased	2	2
Aspartate aminotransferase increased	2	2
Bronchospasm	2	2
Cardiac arrest	2	2
Cyanosis	2	2
Pharyngitis	2	2
Blood pressure decreased	1	.9
Cardiogenic shock	1	.9
Hyperventilation	1	.9
Myalgia	1	.9
Peripheral swelling	1	.9
Pruritus	1	.9
Respiratory distress	1	.9
Seasonal allergy	1	.9
Septic shock	1	.9
Swelling	1	.9
Urticaria	1	.9

Also of note is a postmarketing case description for the patient for record number SRP-000051-2017 who had events (included in the above list) of Cyanosis, Flushing, Infusion related reaction, and Rash. In response to these events, the infusion was stopped, but the patient was later continued on drug. This case is highlighted because it clearly represents a significant hypersensitivity event.

Discussion

The Prior Approval Supplement submitted by the applicant has unique challenges when analyzing the data and context of events. The data to base this consideration are extremely limited both in terms of the absolute number of patients and particularly for the number of placebo patients in the double-blind study, which makes disproportionality analyses very difficult.

The applicant's own analysis is of limited use since it limited its consideration to events occurring on the day of infusion or the day after and also to events considered relevant, which may introduce bias into the analysis. That being said, even the applicant's analyses has yielded some events that were considered serious by the investigator and required medication and/or an emergency room visit.

In considering what my recommendation would be, I considered the following points from the Guidance for Industry, Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format:

- *Adverse events that do not meet the definition of a serious adverse reaction but are otherwise clinically significant because they have implications for prescribing decisions or patient management, should also be included in the Warnings and Precautions section…*
  - *An adverse reaction that may lead to a potentially serious outcome unless the dosage or regimen is adjusted, the drug is discontinued, or another drug is administered to prevent the serious outcome.*

There are at least 3 of the 117 postmarketing patients from my analysis (as described above) with reactions severe enough to stop or temporarily discontinue treatment. One of these is clearly hypersensitivity related and in the other two, a contribution cannot be discounted.

Data from both the applicant's and my own analyses demonstrate that EXONDYS 51 has been associated with events where the dose of drug has been or would be typically be managed by terminating administration and or reducing the dosage of the drug. Additionally, several events required medication intervention (e.g., corticosteroids) and, at least in one case, an emergency room visit for bronchospasm that was considered serious by the investigator.

Another consideration is the vulnerable nature of DMD patients. By the time they are adolescents and young adults, they typically have severe cardiac and pulmonary disease. There are a number of events of shock, which would be very difficult to differentiate whether they are purely cardiogenic or have some etiology related to an anaphylactic event. At the very least, DMD patients who are compromised with respect to their cardiopulmonary systems will be at a greater risk of poor outcomes from hypersensitivity reactions.

Finally, I note that the applicant's proposed wording for labeling for hypersensitivity in Section 6.1 has the basic format of a Warning and Precaution in that it that includes a description of symptoms and a general advisement to initiate medical intervention and consider the risk benefit of the therapy if the symptoms appear; the only difference being where this wording is placed in labeling.

Recommendations

For reasons described above I recommend that the language for hypersensitivity be placed in the Warnings and Precautions section of labeling, with modifications to the Highlights, Section 2, and 6 as appropriate.

The final wording in Section 5.1, after negotiation with the applicant, is as follows:

5.1 Hypersensitivity Reactions
Hypersensitivity reactions, including rash and urticaria, pyrexia, flushing, cough, dyspnea, bronchospasm, and hypotension, have occurred in patients who were treated with EXONDYS 51. If a hypersensitivity reaction occurs, institute appropriate medical treatment and consider slowing the infusion or interrupting the EXONDYS 51 therapy *[see Dosage and Administration (2.3)]*.

III. Appendix – Table of Results from SMQ Analyses

Table 8 SMQ Analyses of Eteplirsen Trial Data

Abdominal pain upper	Abdominal pain	6
Abscess limb	Abscess	1
Ankle fracture	Fracture	1
Arthropod sting	Arthropod bite	1
Catheter site bruise	Catheter site related reaction	2
Catheter site haematoma	Catheter site related reaction	1
Catheter site haemorrhage	Catheter site related reaction	1
Catheter site inflammation	Catheter site related reaction	1
Catheter site pain	Catheter site related reaction	4
Cold urticaria	Urticaria	1
Compression fracture	Fracture	1
Drug eruption	Rash	1
Erythema of eyelid	Erythema	1
Femur fracture	Fracture	4
Foot fracture	Fracture	2
Gastroenteritis viral	Gastroenteritis	3
Humerus fracture	Fracture	1
Incision site erythema	Incision site complication	1
Incision site haemorrhage	Incision site complication	2
Incision site infection	Incision site complication	1
Influenza like illness	Influenza	4
Infusion related reaction	Influenza	1
Infusion site extravasation	Influenza	4
Infusion site haematoma	Influenza	1
Infusion site rash	Rash	1
Infusion site urticaria	Rash	1
Injection site haematoma	Incision site complication	1
Lower limb fracture	Fracture	1
Lumbar vertebral fracture	Fracture	2
Pharyngitis streptococcal	Pharyngitis	1
Productive cough	Cough	2
Radius fracture	Fracture	1
Rash papular	Rash	1
Tibia fracture	Fracture	2
Torus fracture	Fracture	1
Ulna fracture	Fracture	1
Upper respiratory tract congestion	Respiratory tract infection	2
Upper respiratory tract infection	Respiratory tract infection	13
Upper-airway cough syndrome	Cough	1
Viral upper respiratory tract infection	Respiratory tract infection	1

Postmarketing

Table 9 SMQ Analyses of Eteplirsen Postmarketing Data

CASENUM	AEPREF	AEDECODc
SRP-000090-2017	Vascular access site swelling	Vascular access complication
SRP-000026-2017	Vascular access site bruising	Vascular access complication
SRP-000097-2017	Heart rate increased	Tachycardia
SRP-000065-2017	Ischaemic stroke	Stroke
	Cerebral thrombosis	Stroke
SRP-000007-2017	Pseudomonal bacteraemia	Sepsis
SRP-000049-2017	Bacteraemia	Sepsis
SRP-000032-2017	Respiratory arrest	Respiratory failure
SRP-000029-2017	Chronic respiratory failure	Respiratory failure
	Influenza like illness	Influenza
SRP-000033-2017	Rash erythematous	Rash
SRP-000004-2017	Infusion site rash	Rash
	Rash papular	
SRP-000070-2017	Pharyngitis streptococcal	Pharyngitis
SRP-000040-2017	Ulna fracture	Fracture
SRP-000075-2017	Torus fracture	Fracture
SRP-000056-2017	Humerus fracture	Fracture
SRP-000018-2017	Respiration abnormal	Dyspnea
SRP-000029-2017	Upper-airway cough syndrome	Cough
SRP-000029-2017	Productive cough	Cough

Analyses using SMQs related to hypersensitivity

Table 10 Algorithmic Postmarketing

SMQ (Algorithmic Search)	*EXONDYS (N = 117)*				
Level 1	*Events*	*Number of subjects*	*Proportion (%)*	*Proportion C.I. (lower bound) (%)*	*Proportion C.I. (upper bound) (%)*
(1) Anaphylactic reaction	13	5	4.27	1.84	9.62

Table 11 Narrow terms

SMQ (Narrow Search)		*EXONDYS (N = 117)*				
Level 1	*Level 2*	*Events*	*Number of subjects*	*Proportion (%)*	*Proportion C.I. (lower bound) (%)*	*Proportion C.I. (upper bound) (%)*
(1) Hypersensitivity		10	9	7.69	4.1	13.97
(1) Shock		4	3	2.56	0.88	7.27
(1) Shock	(2) Shock-associated circulatory or cardiac conditions (excl torsade de pointes)	3	3	2.56	0.88	7.27
(1) Asthma/bronchospasm		2	2	1.71	0.47	6.02
(1) Angioedema		1	1	0.85	0.15	4.68
(1) Shock	(2) Toxic-septic shock conditions	1	1	0.85	0.15	4.68

Table 12 Broad terms

SMQ (Broad Search)		*EXONDYS (N = 117)*				
Level 1	*Level 2*	*Events*	*Number of subjects*	*Proportion (%)*	*Proportion C.I. (lower bound) (%)*	*Proportion C.I. (upper bound) (%)*
(1) Anaphylactic reaction		41	26	22.22	15.64	30.57
(1) Drug reaction with eosinophilia and systemic symptoms syndrome		27	22	18.8	12.76	26.83
(1) Hypersensitivity		24	19	16.24	10.65	23.98
(1) Eosinophilic pneumonia		7	7	5.98	2.93	11.84
(1) Shock		7	6	5.13	2.37	10.74
(1) Shock	(2) Shock-associated circulatory or cardiac conditions (excl torsade depointes)	6	6	5.13	2.37	10.74
(1) Shock	(2) Toxic-septic shock conditions	4	4	3.42	1.34	8.46
(1) Angioedema		3	3	2.56	0.88	7.27
(1) Asthma/bronchospasm		3	3	2.56	0.88	7.27

(1) Shock	(2) Hypovolaemic shock conditions	3	3	2.56	0.88	7.27
(1) Shock	(2) Anaphylactic/anaphylactoid shock conditions	3	3	2.56	0.88	7.27

APPEARS THIS WAY ON ORIGINAL

References

1. Bircher, A.J. and K. Scherer, *Delayed cutaneous manifestations of drug hypersensitivity*. Med Clin North Am, 2010. **94**(4): p. 711-25, x.
2. Bousquet, P.J., et al., *Clinical presentation and time course in hypersensitivity reactions to beta-lactams*. Allergy, 2007. **62**(8): p. 872-6.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTOPHER D BREDER
02/07/2018

NICHOLAS A KOZAUER
02/07/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 206-488/S-006

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

From:	Paul Alessandro
To:	Choy, Fannie (Yuet)
Cc:	Shamim Ruff
Subject:	RE: FDA Proposed labeling text: re: NDA 206488/S-006
Date:	Thursday, February 08, 2018 10:25:51 AM
Attachments:	image016.png
Importance:	High

Dear Fannie,

I confirm receipt of this correspondence.

Regards,
Paul

Paul Alessandro, MS
Senior Director, Regulatory Affairs
p 617.274.4051 c (b) (6) f 617.812.0509
e palessandro@sarepta.com

SAREPTA THERAPEUTICS
215 First Street, Cambridge, MA 02142 USA

From: Choy, Fannie (Yuet) [mailto:Fannie.Choy@fda.hhs.gov]
Sent: Thursday, February 08, 2018 10:23 AM
To: Paul Alessandro <PAlessandro@Sarepta.com>
Cc: Shamim Ruff <SRuff@Sarepta.com>; Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Subject: [EXTERNAL] RE: FDA Proposed labeling text: re: NDA 206488/S-006
Importance: High

Dear Paul,

We want to inform you that we made the same editorial revision in the Warnings and Precautions section of the Highlights.

We have included a comma after hypotension in this sentence: "Hypersensitivity Reactions: Hypersensitivity reactions, including pyrexia, flushing, cough, dyspnea, bronchospasm, rash, urticaria, and hypotension, have occurred in patients treated with EXONDYS 51."

Kindly confirm receipt of this email.

Regards,
Fannie

Fannie Choy, RPh
Regulatory Project Manager
Division of Neurology Products

From: Paul Alessandro [mailto:PAlessandro@Sarepta.com]
Sent: Wednesday, February 07, 2018 2:51 PM
To: Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Cc: Shamim Ruff <SRuff@Sarepta.com>
Subject: RE: FDA Proposed labeling text: re: NDA 206488/S-006
Importance: High

Dear Fannie,

In response to your February 6 email regarding our pending labeling supplement for NDA 206,488, identified as S-006, please accept this correspondence as our concurrence with the Agency's editorial revision of the labeling text for the proposed PI, which adds a comma after hypotension in the following sentence in Section 5.1: "Hypersensitivity reactions, including rash and urticaria, pyrexia, flushing, cough, dyspnea, bronchospasm, and hypotension, have occurred in patients who were treated with EXONDYS 51."

Please confirm your receipt of this email.

Regards,
Paul

Paul Alessandro, MS
Senior Director, Regulatory Affairs
p 617.274.4051 c (b) (6) f 617.812.0509
e palessandro@sarepta.com

SAREPTA THERAPEUTICS
215 First Street, Cambridge, MA 02142 USA

From: Choy, Fannie (Yuet) [mailto:Fannie.Choy@fda.hhs.gov]
Sent: Tuesday, February 06, 2018 3:34 PM
To: Paul Alessandro <PAlessandro@Sarepta.com>
Cc: Shamim Ruff <SRuff@Sarepta.com>; Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Subject: [EXTERNAL] RE: FDA Proposed labeling text: re: NDA 206488/S-006
Importance: High

Dear Paul:

Please refer to your pending labeling supplement-006 for NDA 206488 for Exondys 51 (eteplirsen).

We have an editorial revision of the labeling text for the proposed PI.

Under Section 5.1, we have included a comma after hypotension in this sentence: "Hypersensitivity reactions, including rash and urticaria, pyrexia, flushing, cough, dyspnea, bronchospasm, and hypotension, have occurred in patients who were treated with EXONDYS 51."

Kindly confirm receipt of this email and provide concurrence at your earliest convenience.

Regards,
Fannie

Fannie Choy, RPh
Regulatory Project Manager
Division of Neurology Products

From: Paul Alessandro [mailto:PAlessandro@Sarepta.com]
Sent: Friday, February 02, 2018 5:31 PM
To: Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Cc: Shamim Ruff <SRuff@Sarepta.com>
Subject: RE: FDA Proposed labeling text: re: NDA 206488/S-006
Importance: High

Dear Fannie,

Thank you and have nice weekend.

Regards,
Paul

Paul Alessandro, MS
Senior Director, Regulatory Affairs
p 617.274.4051 c (b) (6) f 617.812.0509
e palessandro@sarepta.com

215 First Street, Cambridge, MA 02142 USA

From: Choy, Fannie (Yuet) [mailto:Fannie.Choy@fda.hhs.gov]
Sent: Friday, February 02, 2018 5:07 PM
To: Paul Alessandro <PAlessandro@Sarepta.com>
Cc: Shamim Ruff <SRuff@Sarepta.com>; Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Subject: [EXTERNAL] RE: FDA Proposed labeling text: re: NDA 206488/S-006

Dear Paul,

We acknowledge receipt of your February 1, 2018 submission containing the response to the FDA labeling comments. Thank you for the proposed addition of Section 17 verbatim statement. We accept the February 1, 2018 proposed edits. We note some variation in the fonts and will be fixing those.

Regards,
Fannie

Fannie Choy, RPh
Regulatory Project Manager
Division of Neurology Products

From: Paul Alessandro [mailto:PAlessandro@Sarepta.com]
Sent: Thursday, February 01, 2018 4:22 PM
To: Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Cc: Shamim Ruff <SRuff@Sarepta.com>
Subject: RE: FDA Proposed labeling text: re: NDA 206488/S-006
Importance: High

Dear Fannie,

Sorry for the delay in notification; I've been in meetings all day. The proposed labeling revisions were accepted and our response was submitted earlier today. A copy of the cover letter is attached for your convenience.

Again, I apologize for the delay.

Regards,
Paul

Paul Alessandro, MS
Senior Director, Regulatory Affairs
p 617.274.4051 c (b) (6) f 617.812.0509
e palessandro@sarepta.com

SAREPTA THERAPEUTICS
215 First Street, Cambridge, MA 02142 USA

From: Choy, Fannie (Yuet) [mailto:Fannie.Choy@fda.hhs.gov]

Sent: Thursday, February 01, 2018 3:49 PM
To: Paul Alessandro <PAlessandro@Sarepta.com>
Cc: Shamim Ruff <SRuff@Sarepta.com>; Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Subject: [EXTERNAL] RE: FDA Proposed labeling text: re: NDA 206488/S-006
Importance: High

Dear Paul,

I would like to follow up on the status of the proposed labeling for this supplement.

Regards,
Fannie

Fannie Choy, RPh
Regulatory Project Manager
Division of Neurology Products

From: Paul Alessandro [mailto:PAlessandro@Sarepta.com]
Sent: Tuesday, January 30, 2018 4:10 PM
To: Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Cc: Shamim Ruff <SRuff@Sarepta.com>
Subject: RE: FDA Proposed labeling text: re: NDA 206488/S-006
Importance: High

Dear Fannie,

We acknowledge receipt of your correspondence and will respond by Thursday morning, February 1.

Best regards,
Paul

Paul Alessandro, MS
Senior Director, Regulatory Affairs
p 617.274.4051 c (b) (6) f 617.812.0509
e palessandro@sarepta.com

SAREPTA THERAPEUTICS
215 First Street, Cambridge, MA 02142 USA

From: Choy, Fannie (Yuet) [mailto:Fannie.Choy@fda.hhs.gov]
Sent: Tuesday, January 30, 2018 2:38 PM

To: Shamim Ruff <SRuff@Sarepta.com>
Cc: Paul Alessandro <PAlessandro@Sarepta.com>; Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Subject: [EXTERNAL] RE: FDA Proposed labeling text: re: NDA 206488/S-006
Importance: High

Dear Shamim:

Please refer to your pending labeling supplement-006 for NDA 206488 for Exondys 51 (eteplirsen). We also refer to your proposals for the draft labeling submitted on January 29, 2018. Attached please find the FDA proposed labeling text with our comments.

We ask that you provide concurrence by Thursday morning Feb 1, 2018.

Kindly confirm receipt of email.

Regards,
Fannie

Fannie Choy, RPh
Regulatory Project Manager

Center for Drug Evaluation and Research (CDER)
ODE1 | Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-2899
fannie.choy@fda.hhs.gov

From: Choy, Fannie (Yuet)
Sent: Wednesday, January 24, 2018 4:20 PM
To: Shamim Ruff <SRuff@Sarepta.com>
Cc: Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>; Paul Alessandro (palessandro@sarepta.com) <palessandro@sarepta.com>
Subject: FDA Proposed labeling text: re: NDA 206488/S-006
Importance: High

Dear Shamim:

Please refer to your pending labeling supplement-006 for NDA 206488 for Exondys 51 (eteplirsen). Attached please find the FDA proposed labeling text for the package insert.

We have accepted your proposed edits which we agreed, and our additional edits are in tracked changes. Please include any additional proposals in tracked changes in a clean version of this document.

Provide a response by COB Monday, January 29, 2018.

Kindly confirm receipt of email.

Regards,
Fannie

Fannie Choy, RPh
Regulatory Project Manager

Center for Drug Evaluation and Research (CDER)
ODE1 | Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-2899
fannie.choy@fda.hhs.gov

The information contained in this message may be confidential, privileged and protected from disclosure. If the reader of this message is not the intended recipient, you are hereby notified that any dissemination, distr bution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify us immediately by email or telephone and destroy all copies of the original message. Thank you.

The information contained in this message may be confidential, privileged and protected from disclosure. If the reader of this message is not the intended recipient, you are hereby notified that any dissemination, distr bution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify us immediately by email or telephone and destroy all copies of the original message. Thank you.

The information contained in this message may be confidential, privileged and protected from disclosure. If the reader of this message is not the intended recipient, you are hereby notified that any dissemination, distr bution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify us immediately by email or telephone and destroy all copies of the original message. Thank you.

The information contained in this message may be confidential, privileged and protected from disclosure. If the reader of this message is not the intended recipient, you are hereby notified that any dissemination, distr bution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify us immediately by email or telephone and destroy all copies of the original message. Thank you.

The information contained in this message may be confidential, privileged and protected from disclosure. If the reader of this message is not the intended recipient, you are hereby notified that any dissemination, distr bution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify us immediately by email or telephone and destroy all copies of the original message. Thank you.

The information contained in this message may be confidential, privileged and protected from disclosure. If the reader of this message is not the intended recipient, you are hereby notified that any dissemination, distr bution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify us immediately by email or telephone and destroy all copies of the original message. Thank you.

The information contained in this message may be confidential, privileged and protected from disclosure. If the reader of this message is not the intended recipient, you are hereby notified that any dissemination, distr bution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify us immediately by email or telephone and destroy all copies of the original message. Thank you.

The information contained in this message may be confidential, privileged and protected from disclosure. If the reader of this message is not the intended recipient, you are hereby notified that any dissemination, distr bution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify us immediately by email or telephone and destroy all copies of the original message. Thank you.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YUET L CHOY
02/08/2018

From:	Paul Alessandro
To:	Choy, Fannie (Yuet)
Cc:	Shamim Ruff
Subject:	RE: FDA Proposed labeling text: re: NDA 206488/S-006
Date:	Wednesday, February 07, 2018 2:51:10 PM
Attachments:	image006.png
Importance:	High

Dear Fannie,

In response to your February 6 email regarding our pending labeling supplement for NDA 206,488, identified as S-006, please accept this correspondence as our concurrence with the Agency's editorial revision of the labeling text for the proposed PI, which adds a comma after hypotension in the following sentence in Section 5.1: "Hypersensitivity reactions, including rash and urticaria, pyrexia, flushing, cough, dyspnea, bronchospasm, and hypotension, have occurred in patients who were treated with EXONDYS 51."

Please confirm your receipt of this email.

Regards,
Paul

Paul Alessandro, MS
Senior Director, Regulatory Affairs
p 617.274.4051 c (b) (6) f 617.812.0509
e palessandro@sarepta.com

SAREPTA THERAPEUTICS
215 First Street, Cambridge, MA 02142 USA

From: Choy, Fannie (Yuet) [mailto:Fannie.Choy@fda.hhs.gov]
Sent: Tuesday, February 06, 2018 3:34 PM
To: Paul Alessandro <PAlessandro@Sarepta.com>
Cc: Shamim Ruff <SRuff@Sarepta.com>; Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Subject: [EXTERNAL] RE: FDA Proposed labeling text: re: NDA 206488/S-006
Importance: High

Dear Paul:

Please refer to your pending labeling supplement-006 for NDA 206488 for Exondys 51 (eteplirsen). We have an editorial revision of the labeling text for the proposed PI.

Under Section 5.1, we have included a comma after hypotension in this sentence: "Hypersensitivity reactions, including rash and urticaria, pyrexia, flushing, cough, dyspnea, bronchospasm, and hypotension, have occurred in patients who were treated with EXONDYS 51."

Kindly confirm receipt of this email and provide concurrence at your earliest convenience.

Regards,
Fannie

Fannie Choy, RPh
Regulatory Project Manager
Division of Neurology Products

From: Paul Alessandro [mailto:PAlessandro@Sarepta.com]
Sent: Friday, February 02, 2018 5:31 PM
To: Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Cc: Shamim Ruff <SRuff@Sarepta.com>
Subject: RE: FDA Proposed labeling text: re: NDA 206488/S-006
Importance: High

Dear Fannie,

Thank you and have nice weekend.

Regards,
Paul

Paul Alessandro, MS
Senior Director, Regulatory Affairs
p 617.274.4051 c (b) (6) f 617.812.0509
e palessandro@sarepta.com

SAREPTA THERAPEUTICS
215 First Street, Cambridge, MA 02142 USA

From: Choy, Fannie (Yuet) [mailto:Fannie.Choy@fda.hhs.gov]
Sent: Friday, February 02, 2018 5:07 PM
To: Paul Alessandro <PAlessandro@Sarepta.com>
Cc: Shamim Ruff <SRuff@Sarepta.com>; Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Subject: [EXTERNAL] RE: FDA Proposed labeling text: re: NDA 206488/S-006

Dear Paul,

We acknowledge receipt of your February 1, 2018 submission containing the response to the FDA labeling comments. Thank you for the proposed addition of Section 17 verbatim statement. We

accept the February 1, 2018 proposed edits. We note some variation in the fonts and will be fixing those.

Regards,
Fannie

Fannie Choy, RPh
Regulatory Project Manager
Division of Neurology Products

From: Paul Alessandro [mailto:PAlessandro@Sarepta.com]
Sent: Thursday, February 01, 2018 4:22 PM
To: Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Cc: Shamim Ruff <SRuff@Sarepta.com>
Subject: RE: FDA Proposed labeling text: re: NDA 206488/S-006
Importance: High

Dear Fannie,

Sorry for the delay in notification; I've been in meetings all day. The proposed labeling revisions were accepted and our response was submitted earlier today. A copy of the cover letter is attached for your convenience.

Again, I apologize for the delay.

Regards,
Paul

Paul Alessandro, MS
Senior Director, Regulatory Affairs
p 617.274.4051 c (b) (6) f 617.812.0509
e palessandro@sarepta.com

SAREPTA THERAPEUTICS
215 First Street, Cambridge, MA 02142 USA

From: Choy, Fannie (Yuet) [mailto:Fannie.Choy@fda.hhs.gov]
Sent: Thursday, February 01, 2018 3:49 PM
To: Paul Alessandro <PAlessandro@Sarepta.com>
Cc: Shamim Ruff <SRuff@Sarepta.com>; Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Subject: [EXTERNAL] RE: FDA Proposed labeling text: re: NDA 206488/S-006
Importance: High

Dear Paul,

I would like to follow up on the status of the proposed labeling for this supplement.

Regards,
Fannie

Fannie Choy, RPh
Regulatory Project Manager
Division of Neurology Products

From: Paul Alessandro [mailto:PAlessandro@Sarepta.com]
Sent: Tuesday, January 30, 2018 4:10 PM
To: Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Cc: Shamim Ruff <SRuff@Sarepta.com>
Subject: RE: FDA Proposed labeling text: re: NDA 206488/S-006
Importance: High

Dear Fannie,

We acknowledge receipt of your correspondence and will respond by Thursday morning, February 1.

Best regards,
Paul

Paul Alessandro, MS
Senior Director, Regulatory Affairs
p 617.274.4051 c (b) (6) f 617.812.0509
e palessandro@sarepta.com

SAREPTA THERAPEUTICS
215 First Street, Cambridge, MA 02142 USA

From: Choy, Fannie (Yuet) [mailto:Fannie.Choy@fda.hhs.gov]
Sent: Tuesday, January 30, 2018 2:38 PM
To: Shamim Ruff <SRuff@Sarepta.com>
Cc: Paul Alessandro <PAlessandro@Sarepta.com>; Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Subject: [EXTERNAL] RE: FDA Proposed labeling text: re: NDA 206488/S-006
Importance: High

Dear Shamim:

Please refer to your pending labeling supplement-006 for NDA 206488 for Exondys 51 (eteplirsen). We also refer to your proposals for the draft labeling submitted on January 29, 2018. Attached please find the FDA proposed labeling text with our comments.

We ask that you provide concurrence by Thursday morning Feb 1, 2018.

Kindly confirm receipt of email.

Regards,
Fannie

Fannie Choy, RPh
Regulatory Project Manager

Center for Drug Evaluation and Research (CDER)
ODE1 | Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-2899
fannie.choy@fda.hhs.gov

From: Choy, Fannie (Yuet)
Sent: Wednesday, January 24, 2018 4:20 PM
To: Shamim Ruff <SRuff@Sarepta.com>
Cc: Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>; Paul Alessandro (palessandro@sarepta.com) <palessandro@sarepta.com>
Subject: FDA Proposed labeling text: re: NDA 206488/S-006
Importance: High

Dear Shamim:

Please refer to your pending labeling supplement-006 for NDA 206488 for Exondys 51 (eteplirsen). Attached please find the FDA proposed labeling text for the package insert.

We have accepted your proposed edits which we agreed, and our additional edits are in tracked changes. Please include any additional proposals in tracked changes in a clean version of this document.

Provide a response by COB Monday, January 29, 2018.

-

Kindly confirm receipt of email.

Regards,
Fannie

Fannie Choy, RPh
Regulatory Project Manager

Center for Drug Evaluation and Research (CDER)
ODE1 | Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-2899
fannie.choy@fda.hhs.gov

The information contained in this message may be confidential, privileged and protected from disclosure. If the reader of this message is not the intended recipient, you are hereby notified that any dissemination, distr bution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify us immediately by email or telephone and destroy all copies of the original message. Thank you.

The information contained in this message may be confidential, privileged and protected from disclosure. If the reader of this message is not the intended recipient, you are hereby notified that any dissemination, distr bution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify us immediately by email or telephone and destroy all copies of the original message. Thank you.

The information contained in this message may be confidential, privileged and protected from disclosure. If the reader of this message is not the intended recipient, you are hereby notified that any dissemination, distr bution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify us immediately by email or telephone and destroy all copies of the original message. Thank you.

The information contained in this message may be confidential, privileged and protected from disclosure. If the reader of this message is not the intended recipient, you are hereby notified that any dissemination, distr bution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify us immediately by email or telephone and destroy all copies of the original message. Thank you.

The information contained in this message may be confidential, privileged and protected from disclosure. If the reader of this message is not the intended recipient, you are hereby notified that any dissemination, distr bution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify us immediately by email or telephone and destroy all copies of the original message. Thank you.

The information contained in this message may be confidential, privileged and protected from disclosure. If the reader of this message is not the intended recipient, you are hereby notified that any dissemination, distr bution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify us immediately by email or telephone and destroy all copies of the original message. Thank you.

11 page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YUET L CHOY
02/07/2018

From:	Choy, Fannie (Yuet)
To:	Shamim Ruff
Cc:	Paul Alessandro (palessandro@sarepta.com); Choy, Fannie (Yuet)
Subject:	FDA Information Request: re: NDA 206488 / S-006
Date:	Tuesday, January 02, 2018 6:01:55 PM
Attachments:	image001.png
Importance:	High

Dear Shamim:

Please refer to your pending labeling supplement-006 for NDA 206488 for Exondys 51 (eteplirsen) submitted on August 10, 2017. We have the following request for information.

Please send an electronic data file in SAS transport format containing the following information (or as much is available for each patient) for all available post-marketing safety reports for eteplirsen.

- patient unique identifier
- age
- dose
- duration of treatment
- event Preferred Term coded in MedDRA (latest version preferable)
- was event serious (i.e., an SAE)
- was the event associated with an action
    - discontinue medication
    - dose reduction
    - additional medication added

Please send this to the Division by COB on Friday **January 5, 2018**.

Kindly confirm receipt of email and let me know if you have any questions.

Regards,
Fannie

Fannie Choy, RPh
Regulatory Project Manager

Center for Drug Evaluation and Research (CDER)
ODE1 | Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-2899
fannie.choy@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YUET L CHOY
01/03/2018
w/ concurrence: Dr. Nick Kozauer, DNP Clinical TL

Choy, Fannie (Yuet)

From: Choy, Fannie (Yuet)
Sent: Monday, November 06, 2017 5:11 PM
To: Shamim Ruff
Cc: Paul Alessandro (palessandro@sarepta.com); Choy, Fannie (Yuet)
Subject: FDA Information Request: re: NDA 206488 / S-006

Importance: High

Dear Shamim:

Please refer to your pending labeling supplement-006 for NDA 206488 for Exondys 51 (eteplirsen). We have the following information request and ask for a response by COB on Friday, 11/10/17.

Provide the following regarding your Labeling Supplement of 8/10/17, as revised on 10/19/17.

Clinical Study Data

1. Provide an update to your ISS datasets containing information on adverse events (ADAE), subject level (ADSL), concomitant medications (ADCM), medical history (ADMH), and exposure. This should include all studies that are completed and the database locked

    a. Your ADSL dataset must contain only one row per subject

    b. Events should only be included in the studies where they start (do not duplicate if the event extends into another study e.g., a placebo controlled study into an extension study)

2. Include listings of all subjects who are currently in ongoing studies if they experienced any

    a. Serious AEs,

    b. AEs of severe intensity,

    c. Study discontinuation, OR

    d. Dose reduction,

    Listings should including their study name/number, unique subject ID, adverse event (preferred term), action taken, concomitant medications, medical history, and exposure.

3. Provide a summary of all relevant postmarketing cases by adverse event (preferred term), action taken, concomitant medications, medical history, and exposure if these data are available. Provide an electronic copy of all relevant cases as an appendix to this report.

Kindly confirm receipt of email and let me know if you have any questions.

Regards,

Fannie

Fannie Choy, RPh
Regulatory Project Manager

Center for Drug Evaluation and Research (CDER)
ODE1 | Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-2899
fannie.choy@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YUET L CHOY
11/06/2017
w/ concurrence: Dr. Nick Kozauer, DNP Clinical TL

Choy, Fannie (Yuet)

From: Choy, Fannie (Yuet)
Sent: Tuesday, October 24, 2017 1:32 PM
To: Shamim Ruff
Cc: Paul Alessandro (palessandro@sarepta.com); Choy, Fannie (Yuet)
Subject: NDA 206488: Labeling Supplement S-006

Importance: High

Dear Shamim:

Please refer to your NDA 206488 for Exondys 51 (eteplirsen).

On October 19, 2017, we have received your October 19, 2017, amendment to the pending labeling supplement-006 (S-006) submitted on August 10, 2017. In addition to amending the proposed language of the prescribing information (PI) describing hypersensitivity events, (b) (4)

Kindly confirm receipt of email and let me know if you have any questions.

Regards,
Fannie

Fannie Choy, RPh
Regulatory Project Manager

Center for Drug Evaluation and Research (CDER)
ODE1 | Division of Neurology Products
U.S. Food and Drug Administration
Tel: 301-796-2899
fannie.choy@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YUET L CHOY
10/24/2017
w/ concurrence: Dr. Nick Kozauer, DNP Clinical TL

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206488/S-006

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

Sarepta Therapeutics, Inc.
Attention: Shamim Ruff, MSc.
Sr. Vice President, Regulatory Affairs and Quality
215 First Street, Suite 415
Cambridge, MA 02142

Dear Ms. Ruff:

We have received your supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 206488

SUPPLEMENT NUMBER: S-006

PRODUCT NAME: Exondys 51 (eteplirsen) Injection, 50 mg per mL

DATE OF SUBMISSION: August 10, 2017

DATE OF RECEIPT: August 10, 2017

This supplemental application proposes to include language describing hypersensitivity events in the Adverse Reactions section of the prescribing information.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 9, 2017, in accordance with 21 CFR 314.101(a). If the application is filed, the goal date will be **February 10, 2018.**

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have questions, please contact me at (301) 796-796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Fannie Choy, R.Ph.
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YUET L CHOY
08/18/2017