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RESEARCH**

APPLICATION NUMBER:

206488Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template
PMR 3095-1

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # NDA 206488
Product Name: eteplirsen

PMR/PMC Description: In order to verify the clinical benefit of eteplirsen, conduct a 2-year randomized, double-blind, controlled trial of eteplirsen in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. Patients should be randomized to the approved dosage of eteplirsen (30 mg/kg weekly) or to a dosage that provides significantly higher exposure, e.g., 30 mg/kg daily. The primary endpoint will be the North Star Ambulatory Assessment.

PMR/PMC Schedule Milestones:	Draft Protocol Submission:	10/2016
	Final Protocol Submission:	<u>04/2017</u>
	Study/Trial Completion:	<u>11/2020</u>
	Final Report Submission:	<u>05/2021</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Eteplirsen will be approved under the accelerated approval regulations, such that a PMR is required to verify and describe clinical benefit.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Eteplirsen will be approved under the accelerated approval regulations, such that a PMR is required to verify and describe clinical benefit.

The goal of the clinical trial is to verify and describe the effect of eteplirsen on muscle function in patients with Duchenne muscular dystrophy caused by mutations amenable to treatment by exon 51 skipping.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

In order to verify the clinical benefit of eteplirsen, conduct a 2-year randomized, double-blind, controlled trial of eteplirsen in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. Patients should be randomized to the approved dosage of eteplirsen (30 mg/kg weekly) or to a dosage that provides significantly higher exposure, e.g., 30 mg/kg daily. The primary endpoint will be the North Star Ambulatory Assessment.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
An adequate and well-controlled clinical efficacy trial required under the accelerated approval regulations.
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

**EXONDYS 51 (NDA 206488), Rat Carcinogenicity Study
PMR #3095-2**

NDA/BLA # 206488
Product Name: EXONDYS 51™ (eteplirsen) Injection

PMR/PMC Description: A two-year carcinogenicity study of intravenously administered eteplirsen in rat.

PMR/PMC Schedule Milestones:	Draft Protocol Submission:	12/2016
	Final Protocol Submission:	03/2017
	Study Completion:	04/2020
	Final Report Submission:	06/2020

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The application is to be approved and a carcinogenicity study in rat has not been conducted.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A carcinogenicity study in rat is required to identify an unexpected, serious risk of adverse effects of eteplirsen, in accordance with guidance set forth in ICH S1B: *Guidance for Industry S1B Testing for Carcinogenicity of Pharmaceuticals July 1997*.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A two-year carcinogenicity study of intravenously administered eteplirsen in rat.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials

Dosing trials
Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial
(provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

EXONDYS 51 (NDA 206488), Mouse Carcinogenicity Study
PMR # 3095-3

NDA/BLA # 206488
Product Name: EXONDYS 51 (eteplirsen) Injection

PMR/PMC Description: A 26-week carcinogenicity study of eteplirsen, administered by a clinically relevant route, in an appropriate transgenic mouse model.

PMR/PMC Schedule Milestones:	Draft Protocol Submission:	10/2016
	Final Protocol Submission:	<u>01/2017</u>
	Study Completion:	<u>05/2018</u>
	Final Report Submission:	<u>06/2018</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The application is to be approved and a carcinogenicity study in mouse has not been conducted.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A carcinogenicity study in mouse is required to identify an unexpected, serious risk of adverse effects of eteplirsen, in accordance with guidance set forth in ICH S1B: *Guidance for Industry S1B Testing for Carcinogenicity of Pharmaceuticals July 1997*.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A 26-week carcinogenicity study of eteplirsen, administered by a clinically relevant route, in an appropriate transgenic mouse model.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials

Dosing trials
Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial
(provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template
PMC 3095-4

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA #: NDA 206488

Product Name: Exondys 51 (eteplirsen) Injection

PMR/PMC Description:

A study to evaluate:

1. patient immune responses, including IgM and IgG isotypes, to eteplirsen, its induced dystrophin protein, and full length dystrophin;
2. the impact of immune responses on product PK and clinical efficacy and safety.

The assays for antibodies to eteplirsen, the induced dystrophin, and full length dystrophin should be performed with sampling times optimized to detect early, peak, and late antibody responses, and should be fully validated.

3. for subjects whose serum screens positive for antibodies, the samples should be tested for neutralizing activity, to product activity, and/or product uptake. Antibody titer and persistence should be monitored throughout the duration of the study.
4. in patients who seroconvert, antibody levels should be monitored until they return to baseline.
5. for patients developing hypersensitivity responses, assays to evaluate IgE responses including skin testing or RAST assays should be developed and employed.

Until these assays have been fully validated and reviewed by FDA, sufficient samples should be banked and stored under appropriate conditions so as to allow for re-testing if deemed necessary.

PMR/PMC Schedule Milestones:	Draft Protocol Submission:	01/2017
	Final Protocol Submission:	08/2017
	Study/Trial Completion:	12/2017
	Final Report Submission:	02/2018
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Eteplirsen will be approved under the accelerated approval regulations.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the study is to determine the immunogenic potential of eteplirsen in humans. Safety concerns include the possibility of antibodies to dystrophin that could cause or worsen the autoimmune aspects of Duchenne muscular dystrophy. In addition, antibodies to the drug or to dystrophin would decrease efficacy.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A study to evaluate:

1. patient immune responses, including IgM and IgG isotypes, to eteplirsen, its induced dystrophin protein, and full length dystrophin;
2. the impact of immune responses on product PK and clinical efficacy and safety.

The assays for antibodies to eteplirsen, the induced dystrophin, and full length dystrophin should be performed with sampling times optimized to detect early, peak, and late antibody responses, and should be fully validated.

3. for subjects whose serum screens positive for antibodies, the samples should be tested for neutralizing activity, to product activity, and/or product uptake. Antibody titer and persistence should be monitored throughout the duration of the study.
4. in patients who seroconvert, antibody levels should be monitored until they return to baseline.
5. for patients developing hypersensitivity responses, assays to evaluate IgE responses including skin testing or RAST assays should be developed and employed.

Until these assays have been fully validated and reviewed by FDA, sufficient samples should be banked and stored under appropriate conditions so as to allow for re-testing if deemed necessary.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety

- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*
-

(signature line for BLAs)

APPEARS THIS WAY ON ORIGINAL

PMR/PMC Development Template
PMC 3095-5

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # NDA 206488
Product Name: eteplirsen

PMR/PMC Description: Conduct a 2-year controlled trial in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 or 53 skipping with a phosphorodiamidate morpholino oligomer (PMO) designed to bind to a regulatory site governing splicing of the corresponding exon. The trial should include at least two well-separated doses of each PMO, with the high dose designed to provide the greatest dystrophin response possible, based upon preliminary dose-finding, with an expectation of acceptable tolerability. The primary objective of this study will be to evaluate the effect of the two PMO doses (combined-active group) compared to control on the North Star Ambulatory Assessment. The secondary objective will be to evaluate dystrophin levels as percent of normal by Western blot, with tissue to be obtained by needle biopsy.

PMR/PMC Schedule Milestones:	Draft Protocol Submission:	12/2016
	Final Protocol Submission:	<u>04/2017</u>
	Trial Completion:	<u>04/2021</u>
	Final Report Submission:	<u>10/2021</u>
	Other: _____	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Eteplirsen will be approved under the accelerated approval regulations.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Exon skipping therapy is designed to increase dystrophin levels in Duchenne muscular dystrophy, which may result in clinical benefit. There is a need to identify specific populations of patients that may benefit from such treatment.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial:** any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a 2-year controlled trial in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 or 53 skipping with a phosphorodiamidate morpholino oligomer (PMO) designed to bind to a regulatory site governing splicing of the corresponding exon. The trial should include at least two well-separated doses of each PMO, with the high dose designed to provide the greatest dystrophin response possible, based upon preliminary dose-finding, with an expectation of acceptable tolerability. The primary objective of this study will be to evaluate the effect of the two PMO doses (combined-active group) compared to control on the North Star Ambulatory Assessment. The secondary objective will be to evaluate dystrophin levels as percent of normal by Western blot, with tissue to be obtained by needle biopsy.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 Pharmacokinetic studies or clinical trials
 Drug interaction or bioavailability studies or clinical trials
 Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template: Product Quality (CMC)
PMC # 3095-6

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 206488
Product Name: Exondys 51 (eteplirsen injection)

PMC #1 Description: Evaluate possible reasons for the upward trend in assay results from drug product stability studies. Initial investigations are expected to focus on any potential degradants that could co-elute with the main peak, re-authentication of the concentration of the reference standard solution, and quality attributes of the IP-HPLC reagents. Identify any other potential causes for the upward trend observed in the drug product stability.

PMC Schedule Milestones:	Final Protocol Submission:	<u>11/2016</u>
	Study/Trial Completion:	<u>06/2017</u>
	Final Report Submission:	<u>08/2017</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

Eteplirsen is intended for treatment of a debilitating, and ultimately fatal, disease, Duchenne Muscular Dystrophy (DMD), for which there are no approved drugs. Current standard of care includes use of glucocorticoids in conjunction with other palliative interventions. Based on consultation with the clinical division and review of clinical batch history it is considered that the increasing assay trend observed in the drug product stability study would result in minimal risk to patient safety from a quality perspective.

2. Describe the particular review issue and the goal of the study.

During review of the NDA statistical evaluation of assay results from drug product stability studies showed a slight upward trend over time. This is unexpected, since assay results typically remain constant or decrease over time. In order to allow for a viable shelf life, and avoid discarding drug that is otherwise acceptable from a quality and safety perspective, an acceptance criterion of 90-115% for the eteplirsen assay was established. However, unless the root cause for the upward trend on stability is determined, and corrected, additional shelf life extension would be unjustifiable. The goal is to enhance the reliability of future stability studies intended to confirm shelf life and monitor quality of the commercial product.

3. [OMIT – for PMRs only]
4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Evaluate possible reasons for the upward trend in assay results from drug product stability studies. Initial investigations are expected to focus on any potential degradants that could co-elute with the main peak, re-authentication of the concentration of the reference standard solution, and quality attributes of the IP-HPLC reagents. Identify any other potential causes for the upward trend observed in the drug product stability.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

2. Describe the particular review issue and the goal of the study.

During the drug product manufacturing process the concentration of the bulk solution is adjusted to 100% of target based on results for an in-process (b) (4). However, assay results at lot release, which are determined by (b) (4) are consistently slightly higher than target potency. The goal of the study is to ensure that, within normal assay variability, future product lots consistently manufactured at 100% of target potency

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Revalidate the suitability in-process (b) (4) used during drug product manufacture with respect to the accuracy of the method and the robustness of the method in terms of (b) (4). Explore additional possible root causes for the bias in the in-process (b) (4) results and the release (b) (4) assay results that were observed at lot release.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

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

/s/

SALLY U YASUDA
09/16/2016

Memo to File - Amended

Date	9/8/2016
From	Cara Alfaro, Pharm.D., Clinical Analyst, GCPAB/DCCE/OSI Susan Thompson, M.D., Team Leader, GCPAB/DCCE/OSI Kassa Ayalew, M.D., M.P.H., Branch Chief, GCPAB/DCCE/OSI
To	Fannie Choy, Regulatory Project Manager, DNP Christopher Breder, M.D., Medical Officer, DNP Ronald Farkas, M.D., Team Leader, DNP
NDA #	NDA 206488
Applicant	Sarepta Therapeutics Inc.
Drug	eteplirsen
NME	Yes
Therapeutic Classification	Priority Review
Proposed Indication(s)	Treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping
Consultation Request Date	5/3/2016
Summary Goal Date	5/20/2016 (extended)
Action Goal Date	5/26/2016 (extended)
PDUFA Date	5/26/2016 (3-month extension) Final action not yet taken

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The original Memo to File for NDA 206488 contained information regarding three patients in the Leuven Neuromuscular Reference Center (LNRC) in Belgium. This amended Memo to File includes information for six patients from the Italian Duchenne Muscular Dystrophy (DMD) Telethon clinical centers in Italy. There was a delay in scheduling the information-gathering investigations in Italy as permission from local Ethics Committees and informed consent from parents of the patients was required to review de-identified patient information at these six sites.

NDA 206488 included data from two DMD natural history databases as the source of historical control data in support of the efficacy of eteplirsen in the treatment of DMD. The natural history data was obtained from the LNRC in Belgium and the Italian DMD Telethon clinical centers in Italy. This memo to file summarizes the findings of the information-gathering investigation of historical data obtained from these databases.

Data for three historical control DMD patients in the LNRC were reviewed and verified. Apparent discrepancies noted by the review division between the 6-Minute Walking Test (6MWT) and the 10 meter run/walk test for one patient were due to the method used to score

the 6MWT. If patients could not complete the entire 6MWT, it was scored as 0 and not the distance that the patient had actually walked. For three 6MWT assessments for this patient, a 6MWT = 0 did not indicate that the patient was no longer ambulatory. Two of the historical control DMD patients enrolled in clinical trials while in the LNRC; one received an investigational drug and the other received placebo. The review division should consider whether any DMD assessments after the date these patients enrolled in the clinical trials should be considered part of the natural history course for these patients.

The sponsor included data from ten patients in the Italian DMD Telethon in their NDA submission. Data for six of these ten patients were reviewed and verified. Discrepancies were noted between source documents and sponsor data listings for the 6MWT, the 10 meter walk/run, rise time (Gowers maneuver), concomitant steroid use, and frequency and type of physical therapy. One patient refused to perform the 6MWT while a score of 0 was noted in the sponsor data listing which could indicate inability to ambulate. Another patient enrolled in a clinical trial and was randomized to the active treatment group during the time that clinical assessments were obtained. The division should consider whether any DMD assessments after the date this patient was enrolled in the clinical trial should be considered as part of the natural history course.

II. BACKGROUND

Eteplirsen injection (NDA 206488) is being developed for the treatment of Duchenne muscular dystrophy (DMD). Eteplirsen is a phosphorodiamidate morpholino oligomer designed to target the pre-mRNA transcripts of the dystrophin gene so that exon 51 is excluded (or skipped) from the mature, spliced mRNA restoring the reading frame and enabling the production of a shortened, but functional dystrophin protein. This includes patients with deletions of exon 50, 45-50, 47-50, 49-50, 52, and 52-63 of this gene or approximately 13% of all patients with DMD. The proposed indication for eteplirsen is for the treatment of “Duchenne muscular dystrophy in patients who have a confirmed DMD mutation amenable to exon 51 skipping therapy.”

Studies 4658-US-201 (Study 201) and 4658-US-202 (Study 202) were submitted to support the efficacy and safety of eteplirsen in the treatment of DMD. Study 201 was a double-blind, randomized, placebo-controlled 28-week study evaluating intravenous infusions of eteplirsen (30 or 50 mg/kg once per week) or placebo in 12 male subjects with DMD mutations amenable to exon 51 skipping. Study 202 is an ongoing open-label, 212 week extension study for subjects who completed Study 201.

The functional efficacy endpoints included in Studies 201 and 202 were the 6-Minute Walking Test (6MWT) (primary functional efficacy endpoint), the North Star Ambulation Assessment (NSAA), as well as other assessments. The placebo-controlled study (Study 201) failed to demonstrate statistically significant differences between eteplirsen (n = 8) and placebo (n = 4) on the 6MWT and NSAA. The sponsor proposed to evaluate longer term efficacy in subjects administered eteplirsen in the open-label extension study (n = 12, Study 202) with a

comparison group of historical controls (n = 13) receiving standard of care identified from two natural history DMD databases, the Italian DMD Telethon and the Leuven Neuromuscular Reference Center (LNRC) in Belgium. Data for ten historical control patients from the Italian DMD Telethon were provided to the sponsor by Eugenio Mercuri, M.D., Ph.D. and data for three historical control patients from the Leuven Neuromuscular Research Center were provided to the sponsor by Nathalie Goemans, M.D. The sponsor identified historical control patients who could be matched with subjects from Study 202 on specific characteristics including glucocorticoid use at baseline, sufficient longitudinal data for 6MWT, age ≥ 7 years, genotype amenable to any exon skipping therapy, and genotype amenable to exon 51 skipping therapy. Functional assessments, including the 6MWT and NSAA, were performed as part of the clinical assessment of patients used as historical controls.

The sponsor evaluated the 6MWT results comparing subjects from Study 202 to these historical controls over a 36 month time period. Both groups reportedly had decreases in 6MWT from baseline to 36 months. According to the sponsor, subjects in the eteplirsen group (Study 202) had a 6MWT = 263 meters compared to patients in the historical control group who had a 6MWT = 98.5 meters ($p = 0.009$) at 36 months. The sponsor reported that the mean change at 36 months was -100 meters in the eteplirsen group (Study 202) and -251 meters in the historical control group. Over the 36 month period, 6 patients in the historical control group lost the ability to ambulate (6MWT = 0) compared to 2 subjects in the eteplirsen group.

The focus of this assignment was to verify the data that the sponsor has submitted for the historical control group in Belgium and Italy. Specifically, for patients with 6MWT = 0, it was important to verify loss of ambulation (vs. refusal to cooperate) via review of any relevant and available source documents (e.g. progress notes, physical therapy, etc.). Additionally, verification of patient characteristics used to match subjects in Study 202 was considered important (e.g. age, glucocorticoid use) as well as the type and frequency of physical therapy received.

This memo to file summarizes the information-gathering investigation of the three patients from the LNRC and six of the ten patients from the Italian DMD Telethon used as historical controls to compare to subjects enrolled in Study 202. The information gathering primarily included review of original hospital records with a focus on the 6MWT (primary functional efficacy endpoint) and other assessments included in hospital records.

III. Investigated Site and Results:

Name of Physician/Address	Number of Patients	Inspection Date
Nathalie Goemans, M.D. University Hospitals Leuven, Dept. of Child Neurology Herestraat 49 B-3000 Leuven, Belgium	3	4/25/16
Giovanni Baranello, M.D. Istituto Neurologico Carlo Besta Via Giovanni Celoria11, 20133 Milan, Italy	1	8/1/2016
Stefano Previtali, M.D. Ospedale San Raffaele Via Olgettina 60, 20132 Milan, Italy	1	8/1/2016
Roberta Battini, M.D. IRCCS Fondazione Stella Maris Pisa Viale del Tirreno 331, 56128 Pisa, Italy	1	8/2/2016
Adele D'Amico, M.D. Ospedale Bambino Gesù Viale Fernandino Baldelli n. 41 Rome, Italy	1	8/3/2016
Professor Tiziana Mongini Department of Neurosciences University of Torino AOU SG Battista Torino Via Cherasco15, 10126 Torino, Italy	2	8/4/2016

Physician: Nathalie Goemans, M.D.; Belgium

Three patients from the Leuven Neuromuscular Reference Center were used as historical controls to compare to subjects enrolled in Study 202. Records reviewed included informed consent documents, genetic test results, and electronic medical records. The electronic medical records included results of the 6MWT, 10 meter run/walk, rise time (rise from floor/Gower's) and climb four stairs assessments and the frequency of physical therapy. (b) (4)

(b) (4) Dr. Goemans indicated that she did not have any other (b) (4)

financial holdings in Sarepta Therapeutics, Inc.

For the 3 DMD patients, physiotherapists conducted the 6MWT, 10 meter walk/run, rise time, and climb four stairs assessments. The majority of the assessments were performed by one of the two physiotherapists. The physiotherapists were trained to conduct the 6MWT, rise from floor, and 10 meter run assessments according to a standard protocol. Assessments were performed in the Physiotherapy Department. The 6MWT was performed during routine standard of care visits beginning in 2011/2012.

The 6MWT test area was marked with a 25-meter tape line starting at one cone extending to a second cone. As a safety measure, one assistant followed the patient during the assessment and the clinical evaluator documented the laps walked. The distance from one cone to the other was 25 meters or one lap. Positive verbal encouragement was given during the testing. According to Dr. Goemans, when the 6MWT assessments were first used, a score of 0 was recorded if the assessment was not completed in full. For 6MWT assessments that are currently performed, however, if the test is not completed, the total length walked is recorded.

Data Verification for Patient (b) (6)

(b) (6) was an (b) (6) male with DMD at the time the first 6MWT was performed on 6/18/2009.

- Genetic testing was performed by the University Hospital Leuven. The patient had deletion of exon 50 in the DMD gene which was verified.
- The 6MWT, 10 meter run/walk, rise time, and NSAA scores in the data listings were compared to source documents. The data submitted for this patient included three visits in which the 6MWT = 0 while the 10 meter run/walk test was a recorded value (see Table 1). The 6MWT was given a score of 0 on two visits in which the patient was still ambulatory and able to complete the 10 meter run/walk, but could walk only short distances. In another visit, the 6MWT was given a score of 0 since the patient did not complete the entire six minute assessment though he was able to walk 125 meters during the assessment. The patient's non-ambulatory status was confirmed at the 9/29/2011 visit.

Table 1. Patient (b) (6): Dates of Visit, 6MWT, 10Meter Walk/Run Assessments and Reviewer Comments

Visit Date	6MWT (meters)	10 Meter Run/Walk (seconds)	Comments
6/18/2009	327	6.84	
1/14/2010	0	11.02	Patient remained ambulatory but only walks short distances and is afraid of falling
7/22/2010	0	10.85	Did not complete 6MWT; able to walk 125 meters in 3.28 minutes. After stopping, he no longer wanted to continue due to back pain.
3/10/2011	0	13.14	Patient was unable to walk 25 meters (distance between the two cones on 6MWT)
6/27/2011			Patient was evaluated for participation in a non-ambulatory DMD trial
9/29/2011	0	unable	Patient no longer able to walk and used an electric wheelchair Medical record "we still have not received any information to date regarding the study and continue to wait".

- Source documents indicated that the 10 meter run/walk was 6.46 seconds and the rise time was 20.40 seconds at the 2/26/2008 visit. In the data listing, there is no score listed for the 10 meter run/walk and the score for the rise time is 6.46.
- Source documents indicate the patient received deflazacort 6 mg from November 2005 through March 6, 2006 due to a misunderstanding in dosage by the patient's mother. The dose was later corrected to deflazacort 21 mg beginning March 7, 2006 and continuing.
- The field verified that data noted to be redacted from the 2/26/2008 source document was the patient's name.
- This patient was receiving physical therapy two to three times per week at school and once per week at home in 2010 and five times per week in 2011.

Data Verification for Patient (b) (6)

(b) (6) was an (b) (6) male with DMD at the time the first 6MWT was performed on 6/23/2009.

- Genetic testing was performed by the University Hospital Leuven. The patient had deletion of exon 52 in the DMD gene which was verified.

- The 6MWT, 10 meter run/walk, rise time, climb four stairs, and NSAA scores in the data listings were verified with source documents. 6MWT results submitted for this patient were verified against source documents and are provided in Table 2. The inspection of source documents verified that the patient entered a clinical study after 9/19/2011 and was randomized to investigational drug. No further information regarding this clinical study is available. The 6MWT results after the patient was enrolled in the clinical study were 252, 240, and 50 meters. The inspection verified that the patient lost ambulation and become unable to perform the 10 meter run/walk at a visit on 12/13/2012 after he was enrolled in a clinical study.

Table 2. Patient ^{(b) (6)}: Dates of Visit, 6MWT and Reviewer Comments

Visit Date	6MWT (meters)	Comments
6/23/2009	451	
10/13/2009	425	
4/27/2010	421	
10/26/2010	378	
5/5/2011	320	
9/19/2011	252	Patient entered a clinical study after 9/19/2011, randomized to investigational drug
3/6/2012	240	
7/30/2012	50	
12/13/2012	0	Verified loss of ambulation, still participating in a clinical trial
6/25/2013	0	

- The inspection verified that this patient began taking deflazacort 30 mg daily (rather than intermittently) in September 2008 as verified by medical records.
- This patient received daily physical therapy starting in 2010.

Data Verification for Patient ^{(b) (6)}

^{(b) (6)} was an ^{(b) (6)} male with DMD at the time the first 6MWT was performed on 5/4/2010.

- Genetic testing was performed by the University Hospital Leuven. The patient had deletion of exons 45-50 in the DMD gene which was verified

- The 6MWT, 10 meter run/walk, rise time, climb four stairs, and NSAA scores in the data listings were verified with source documents. 6MWT results submitted for this patient and verified against source documents are provided in Table 3. The field noted that the patient began participation in the placebo arm of a clinical trial after the 5/16/2011 visit. No further information regarding this clinical study is available. This patient had a 6MWT = 0 at the 11/24/2014 visit and was unable to perform the 10 meter run/walk assessment. The field verified that, according to medical records, loss of ambulation occurred in 10/2014 and long leg braces were applied in 11/2014 to assist in standing.

Table 3. Patient ^{(b) (6)}: Dates of Visit, 6MWT and Reviewer Comments

Visit Date	6MWT	Comments
5/4/2010	355	
9/9/2010	328	
5/16/2011	375	Patient participated in clinical trial after this visit; received placebo
8/8/2011	378	
1/24/2012	352	
4/16/2012	320	
12/13/2013	225	
11/24/2014	0	Loss of ambulation occurred in 10/2014, long leg braces were applied in 11/2014 to assist in standing

- This patient received physical therapy beginning in January 2006. The frequency of physical therapy was once per week at home in 2009.

Reviewer Comments

The historical control data from the LNRC submitted by Sarepta Therapeutics in NDA 206488, specifically the 6MWT, 10 meter walk/run, rise time, and NSAA results were verified. The apparent discrepancies between the 6MWT and 10 meter walk/run results for patient ^{(b) (6)} were due to the method used to calculate the 6MWT score. For the 6MWT, patients who were unable to complete the entire 6 minute assessment were given a score of 0 (zero) and not the score reflecting the actual distance that they completed during this assessment. Patients who could not walk at least 25 meters (the distance between the two cones in the 6MWT) were also scored a 0. Therefore, for at least three assessments for patient ^{(b) (6)} a 6MWT = 0 did not indicate inability to ambulate. For their analyses, the sponsor compared the 6MWT results from the historical control patients to the subjects in Study 202. If the patients were able to walk a specific distance, yet the value was recorded as 0 since the patient could not complete the entire 6MWT assessment, this could underestimate 6MWT results for the historical control patients. If distances are available for subjects not completing the entire 6MWT assessment, the division might wish to consider these data in their efficacy analyses.

DMD assessments are available for patient ^{(b) (6)} from 2009 until 2013. However, this patient

entered a clinical study in 2011 and was randomized to investigational drug. This patient lost his ability to ambulate in 2012, while receiving investigational drug. The review division should consider whether any DMD assessments after the date the patient enrolled in this clinical trial should be considered part of the natural history course for this patient.

DMD assessments were available for patient (b) (6) from 2010 until 2014, however, this patient entered a clinical study in 2011. Though this patient received placebo during this clinical study, participation in a study may impact the natural history course for this patient (e.g. motivation of patient/staff, etc.). The review division should consider whether any DMD assessments after the date the patient enrolled in this clinical trial should be considered part of the natural history course for this patient.

Data Verification for Patients in Italian DMD Telethon

Through the respective Ethics Committees and consent obtained from parents of patients who participated in the Italian DMD Telethon, permission was granted for the FDA to review de-identified records for six of the ten patients included in the sponsor's NDA submission. Records for patients (b) (6) were reviewed. Records for four patients could not be reviewed since either approval from the corresponding Ethics Committees had not been received or parents did not provide consent. The information-gathering inspection compared source documents with sponsor data listings for the 6MWT, NSAA, 10 meter walk/run, rise time (Gowers maneuver), concomitant steroid use, and frequency of physical therapy. Discrepancies noted during the inspection are detailed in Tables 4 to 8.

Administration of the 6MWT and NSAA assessments were performed by physical therapists who, with the exception of one, were not available for interviews at the time of the inspections. Descriptions of assessments were provided by physicians who were not typically present to observe the assessments.

- According to physicians at most of the sites, patients attempted the rise time (Gowers maneuver) without support. If support was used (e.g. a chair), this was reflected in the score.
- The order of the NSAA and 6MWT assessments was not standardized nor was the rest period standardized between these assessments. For all but one of the sites, the NSAA was performed first followed by the 6MWT. The duration of rest time between these assessments was variable among the sites with an unspecified rest time, 10 minute rest time, or at least a 30 minute rest time.

Discrepancies between source documents and data listings for the 6MWT, 10 meter walk/run time, and rise time are noted in Tables 4 to 6. Of note, at his 36 month visit, patient TO 6 was able to walk but refused to perform the 6MWT. The data listing for this visit denotes a 0 for the 6MWT which could be interpreted as loss of ambulation. The data listing does include a 10 meter walk/run result for this 36 month visit. There were no discrepancies noted for NSAA assessments.

Patient (b) (6) participated in a clinical trial beginning on 6/20/2011 (24 month visit), and he was randomized to the active treatment group. Data listings provide 6MWT and NSAA assessments for the 36 month visit, after this patient had been participating in a clinical trial for 18 months.

The NSAA scoring sheet included a line for each of 17 assessments. Items were scored 0, 1, or 2 and some of the assessments were also timed. On most of these data sheets, the column for timed items had boxes to record times for completion of the 10 meter walk (item 2) and rise from floor (rise time or Gowers maneuver), item 11; the boxes for the remaining NSAA assessments were grayed out so that times could not be recorded. However, for some of the data sheets, boxes to record times were available for all 17 assessments (e.g. no boxes were grayed out). At least one physician had recorded times for all assessments and some physicians recorded times for run (10 meter run, item 17). The review division wanted to clarify whether the times entered for the 10 meter walk were walk times or run times. Physicians were asked how the 10 meter walk/run was assessed. Some physicians stated that, although the box for timing is next to the walking assessments, physical therapists would always record the time of the run test, and the patient was instructed to go as fast as he could. One physician stated that for the 10 meter walk test, the patient was instructed to walk as fast as he could but not to run. It appears that the 10 meter walk test and the 10 meter run test were not standardized and some physicians may have recorded 10 meter run times in the 10 meter walk time assessment.

Concomitant steroid use and physical therapy orders were noted in the records provided, but documentation to support compliance with these orders was not available. There was considerable discrepancies noted between the source documents and data listings for concomitant steroid use and physical therapy as noted in Tables 7 and 8.

The approximate date for loss of ambulation was able to be determined for four of the patients. (b) (6) lost ambulation in July 2014, PI 3 lost ambulation in February 2012, (b) (6) lost ambulation between 9/12/2012 and 6/20/2013, and (b) (6) lost ambulation between 7/12/2010 and 3/14/2011.

Table 4. Six Minute Walk Test (6MWT)

Subject ID	Date/Interval	6MWT (meters)		Comments
		Source	Data Listing	
(b) (6)	6 months	317	317	Noted as 12 month visit in data listing
	15 months	Unable to perform	0	Noted as 24 month visit in data listing
	24 months	Unable to perform	0	Noted as 36 month visit in data listing
(b) (6)	19 months	395	395	Noted as 12 month visit in data listing
	36 months	Subject refused	0	Subject was able to walk but refused to perform 6MWT

Table 5. 10 Meter Walk/Run

Subject ID	Date/Interval	10 Meter Walk/Run (seconds)		Comments
		Source	Data Listing	
(b) (6)	1/10/2013 42 months	12	Not performed	Noted as 36 month visit in data listing
(b) (6)	9/15/2011 30 months	15''59	Not performed	Noted as 24 month visit in data listing
(b) (6)	11/9/2009 Baseline	23	No data	
	12/2/2010 12 months	15	No data	
	6/20/11 18 months	11''32	No data	Noted as 24 month visit in data listing Enrolled into clinical study 6/20/2011.
(b) (6)	15 months	35	Unable	Noted as 24 month visit in data listing
(b) (6)	Baseline	18	8	
	19 months	10	8	Noted as 12 month visit in data listing
	25 months	9	10	Noted as 24 month visit in data listing

Table 6. Rise Time (Gowers Maneuver)

Subject ID	Date/Interval	Rise Time (seconds)		Comments
		Source	Data Listing	
(b) (6)	12/4/2013 36 months	0, unable to rise	Not performed	
(b) (6)	9/11/2015 30 months	20''32	Not performed	Noted as 24 month visit in data listing
(b) (6)	11/9/2009 Baseline	6''	No data	
	12/2/2010 12 months	26''17	No data	
	6/20/11 18 months	Unable to rise = 0	No data	Noted as 24 month visit in data listing
(b) (6)	Baseline	10	check	The data listing contains "check" and no numerical value
(b) (6)	19 months	16	10	Noted 12 month visit in data listing
	25 months	18	16	Noted as 24 month visit in data listing

Table 7. Concomitant Steroids

Subject ID	Date/Interval	Steroid*	
		Source	Data Listing
(b) (6)	Baseline to 36 months	deltacortene every other day; dose ranged from approx. 0.45 to 0.9 mg/kg/day	prednisone intermittent, 0.75 mg/kg/day
(b) (6)	Baseline to 36 months	deflazacort; daily for first 20 days of the month; dose ranged from 0.3 to 0.65 mg/kg Four month suspension in dosing due to gastritis	deflazacort intermittent, 0.9 mg/kg/day
(b) (6)	Baseline to 24 months	deltacortene 17.25 mg/day (approx. 0.5 to 0.7 mg/kg/day)	deltacortene, 17.5 mg daily (0.7 mg/kg/day at baseline; 0.5 mg/kg/day at 12 months)
	24 to 36 months	deltacortene 18.75 mg/day (approx. 0.375 to 0.5 mg/kg/day)	deltacortene 18.75 mg daily (0.5 mg/kg/day)
(b) (6)	Baseline to 18 months	deflazacort 25 to 27 mg/day (approx. 0.625 to 0.8 mg/kg/day)	deflazacort 0.9 mg/day, from baseline to 36 months
(b) (6)	Baseline to 24 months	prednisone 25 mg every other day (approx. 0.3 to 0.4 mg/kg/day)	prednisone intermittent, 0.75 mg/kg/day Baseline to 36 months
(b) (6)	Baseline to 36 months	deltacortene 20 to 30 mg every other day (approx. 0.375 mg/kg/day)	prednisone intermittent, 0.75 mg/kg/day

*Deltacortene (brand name) = prednisone (generic name)

Table 8. Physical Therapy

Subject ID	Date/Interval	Physical Therapy	
		Source	Data Listing
(b) (6)	11/3/2010 Baseline	3 times/week	2 times/week
	2/4/2013 36 months	4 times/week and psychometry 2 times/week	2 times/week
(b) (6)	Baseline to 6 months	2 times/week and swimming 1 to 2 times/week	5 times/week Swimming once per week

Subject ID	Date/Interval	Physical Therapy	
		Source	Data Listing
(b) (6)	Baseline to 12 months	6 times/week and swimming 2 times/week	2 times/week swimming once per week
	12 months to 36 months	Once per week and swimming 2 times/week	2 times/week Swimming once per week
(b) (6)	Baseline to 18 months	3 times/week, Parents stretching nightly, Swimming encouraged	5 times/week, Parents stretching 2 times/week
(b) (6)	Baseline to 24 months	Once per week Parents stretching	2 times/week Parents stretching daily, Swimming once per week
(b) (6)	Baseline to 24 months	Once per week, Parents stretching daily	2 times/week, parents stretching daily, swimming once per week

Reviewer Comments

The historical control data from the Italian DMD Telethon submitted by Sarepta Therapeutics in NDA 206488, specifically the NSAA, 6MWT, 10 meter walk/run, rise time, concomitant steroid therapy, and physical therapy were compared with source documents for six of the ten patients included in the submission. Discrepancies between source documents and data listings were noted for all data with the exception of NSAA assessments. One patient, (b) (6), was enrolled in a clinical trial and received active treatment; data listings include 6MWT and NSAA assessments at the 36 month visit when this patient had been in a clinical trial for 18 months. The review division should consider whether any DMD assessments after the date the patient enrolled in this clinical trial should be considered part of the natural history course for this patient.

cc:

Central Document Room/NDA 206488
DNP /Division Director/Billy Dunn
DNP/Deputy Division Director/Eric Bastings
DNP /Medical Team Leader/Ronald Farkas
DNP Medical Officer/Christopher Breder
DNP /Project Manager/Fannie Choy
OSI/Office Director (Acting)/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Susan Thompson
OSI/DCCE/GCPAB Reviewer/Cara Alfaro
OSI/ GCPAB Program Analysts/Joseph Peacock/Yolanda Patague
OSI/Database Project Manager/Dana Walters

{See appended electronic signature page}

Cara Alfaro
Clinical Analyst
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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/s/

CARA L ALFARO
09/08/2016

SUSAN D THOMPSON
09/08/2016

KASSA AYALEW
09/08/2016

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: July 14, 2016

To: Billy Dunn, M.D., Director
Division of Neurology Products (DNP)

Ronald Farkas, M.D., Team Leader, DNP

Christopher Breder, M.D., Medical Officer, DNP

Tracy Peters, Acting Associate Director for Labeling, DNP

Yuet Choy, Regulatory Project Manager, DNP

From: Aline Moukhtara, RN, MPH, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Mathilda Fienkeng, PharmD, Team Leader, OPDP

Subject: OPDP labeling comments for EXONDYS 51 (eteplirsen) injection,
for intravenous use - NDA 206488

On August 25, 2015, DNP consulted OPDP to review the draft Prescribing Information (PI), and carton and container labeling for EXONDYS 51 (eteplirsen) injection, for intravenous use (Exondys 51).

PI

OPDP's review of the proposed PI is based on the substantially complete version of the PI received from DNP (Yuet Choy) via electronic mail on July 12, 2016. OPDP's comments on the draft PI are provided below.

Carton and Container Labeling

OPDP has reviewed the proposed carton and container labeling (attached below) submitted to the electronic document room on March 28, 2016, and we do not have any comments.

If you have any questions, please contact Aline Moukhtara at (301) 796-2841 or Aline.Moukhtara@fda.hhs.gov.

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/s/

ALINE M MOUKHTARA
07/14/2016

M E M O R A N D U M

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: July 13, 2016

TO: Billy H. Dunn, M.D.
Director, Division of Neurology Products
Office of Drug Evaluation-1

FROM: Young Moon Choi, Ph.D.
Deputy Director (Acting)
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

William H. Taylor, Ph.D.
Associate Director
Office of Study Integrity and Surveillance
Office of Translational Sciences

Sean Kassim, Ph.D.
Director
Office of Study Integrity and Surveillance
Office of Translational Sciences

SUBJECT: Review of EIR covering NDA 206488 (AVI 4658;
Eteplirsen)

Recommendation

At the request of the Office of Drug Evaluation-1, Office of Study Integrity and Surveillance (OSIS) conducted inspections at (b) (4) and Sarepta Therapeutics Inc. in Corvallis, OR. The inspections confirmed that the blinding procedure, handling of the sample shipment, and the conduct of Western blot analyses of the samples from study PROMOVI 4658-301 were consistent as predefined in the protocol.

During the inspections, no objectionable observations were found at either site and no Form FDA-483 was issued at the conclusion of the inspections. Following review of the inspectional findings, this reviewer recommends that the study results from the audited study are acceptable for further Agency review.

Inspection

The current inspection was for Study SR-CR-16-003, the interim pharmacodynamics analysis of the ongoing clinical trial, PROMOVI 4658-301.

Study Number: SR-CR-16-003

Study Title: Western Blot Interim Analysis of Novel Dystrophin Expression in Muscle Biopsy Samples from Week 48 of the Clinical Study 4658-301

The tissue processing and blinding of the subject samples from study 4658-301 for Western blot analysis were performed at the

(b) (4)
Dr. William H. Taylor (OSIS) was present at the site and observed the site personnel performing tissue sectioning. He confirmed that the site adhered to the predefined protocol for tissue processing and blinding process. Dr. Taylor examined tracking of biopsy samples and tissue slices and noted no discrepancies or inconsistencies in patient codes or sample identifications. He also did not have any concerns on storage and handling of the biopsy tissue slices. No adverse finding was observed during packaging and shipment of the samples to Sarepta Therapeutics, Inc. located at 4575 SW Research Way, Corvallis, OR, where the Western blot analysis of dystrophin protein levels in patient and control samples were conducted.

The inspection at Sarepta Therapeutics Inc. in Corvallis, OR was conducted by ORA investigator Mark W. Babbitt (b) (4), Ashutosh Rao, Ph.D. (Office of Biotechnology Products), and Young Moon Choi, Ph.D. (OSIS) from 6/20/2016 to 6/23/2016.

Tissue sample handling and blinding/randomization processes were audited by Mr. Babbitt and Dr. Choi. Western blot analysis of tissue lysates were audited by Dr. Rao.

During the inspection, no objectionable conditions were identified. At the conclusion of the inspections, Form FDA-483 was not issued.

Conclusion:

Following review of the inspectional findings, this reviewer recommends that the study results from Study SR-CR-16-003 are acceptable for further Agency review.

Young Moon Choi, Ph.D.
Deputy Director (Acting)
Division of Generic Drug Bioequivalence
Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

Final Classification:

[REDACTED] (b) (4)

NAI: Sarepta Therapeutics, Inc., Corvallis, OR
FEI: 3009712573

CC:
OSIS/Kassim/Taylor
OSIS/PMT/Fenti-Stewart/Nhik/Turner-Rinehardt
OSIS/DGDBE/Cho/Choi
OBP/Rao
CDER/ODE-1/DNP/Choy
ORA [REDACTED] (b) (4)/Babbitt

Draft: YMC 7/12/2016
Edit: JC 7/12/2016
Files # BE 7227

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical Sites/ Sarepta Therapeutics Inc/

FACTS: [REDACTED] (b) (4) **11648400**

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/s/

YOUNG M CHOI
07/13/2016

SEONGEUN CHO
07/13/2016

WILLIAM H TAYLOR
07/13/2016

SEAN Y KASSIM
07/13/2016

Memo to File

Date	5/23/2016
From	Cara Alfaro, Pharm.D., Clinical Analyst, CGPAB/DCCE/OSI Susan Thompson, M.D., Team Leader, CGPAB/DCCE/OSI Kassa Ayalew, M.D., M.P.H., Branch Chief, CGPAB/DCCE/OSI
To	Fannie Choy, Regulatory Project Manager, DNP Christopher Breder, M.D., Medical Officer, DNP Ronald Farkas, M.D., Team Leader, DNP
NDA #	NDA 206488
Applicant	Sarepta Therapeutics Inc.
Drug	eteplirsen
NME	Yes
Therapeutic Classification	Priority Review
Proposed Indication(s)	Treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping
Consultation Request Date	5/3/2016
Summary Goal Date	5/20/2016
Action Goal Date	5/26/2016
PDUFA Date	5/26/2016 (3-month extension)

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

NDA 206488 included data from two Duchenne muscular dystrophy (DMD) natural history databases as the source of historical control data in support of the efficacy of eteplirsen in the treatment of DMD. The natural history data was obtained from the Leuven Neuromuscular Reference Center (LNRC) in Belgium and the Italian DMD Telethon clinical centers in Italy. This memo to file summarizes the findings of the information-gathering investigation of historical data obtained from the LNRC in Belgium. The investigation of the data obtained from Italian DMD patients to support the application is pending.

Data for three historical control DMD patients in the LNRC were reviewed and verified. Apparent discrepancies noted by the review division between the 6-Minute Walking Test (6MWT) and the 10 meter run/walk test for one patient were due to the method used to score the 6MWT. If patients could not complete the entire 6MWT, it was scored as 0 and not the distance that the patient had actually walked. For three 6MWT assessments for this patient, a 6MWT = 0 did not indicate that the patient was no longer ambulatory. Two of the historical control DMD patients enrolled in clinical trials while in the LNRC, one received an investigational drug and the other received placebo. The division should consider whether any DMD assessments after the date these patients enrolled in the clinical trials should be considered part of the natural history course for these patients.

II. BACKGROUND

Eteplirsen injection (NDA 206488) is being developed for the treatment of Duchenne muscular dystrophy (DMD). Eteplirsen is a phosphorodiamidate morpholino oligomer designed to target the pre-mRNA transcripts of the dystrophin gene so that exon 51 is excluded (or skipped) from the mature, spliced mRNA restoring the reading frame and enabling the production of a shortened, but functional dystrophin protein. This includes patients with deletions of exon 50, 45-50, 47-50, 49-50, 52, and 52-63 of this gene or approximately 13% of all patients with DMD. The proposed indication for eteplirsen is for the treatment of “Duchenne muscular dystrophy in patients who have a confirmed DMD mutation amenable to exon 51 skipping therapy.”

Studies 4658-US-201 (Study 201) and 4658-US-202 (Study 202) were submitted to support the efficacy and safety of eteplirsen in the treatment of DMD. Study 201 was a double-blind, randomized, placebo-controlled 28-week study evaluating intravenous infusions of eteplirsen (30 or 50 mg/kg once per week) or placebo in 12 male subjects with DMD mutations amenable to exon 51 skipping. Study 202 is an ongoing open-label, 212 week extension study for subjects who completed Study 201.

The functional efficacy endpoints included in Studies 201 and 202 were the 6-Minute Walking Test (6MWT) (primary functional efficacy endpoint), the North Star Ambulation Assessment (NSAA) as well as other assessments. The placebo-controlled study (Study 201) failed to demonstrate statistically significant differences between eteplirsen (n = 8) and placebo (n = 4) on the 6MWT and NSAA. The sponsor proposed to evaluate longer term efficacy in subjects administered eteplirsen in the open-label extension study (n = 12, Study 202) with a comparison group of historical controls (n = 13) receiving standard of care identified from two natural history DMD databases, the Italian DMD Telethon and the Leuven Neuromuscular Reference Center (LNRC) in Belgium. Data for eight historical control patients from the Italian DMD Telethon were provided by Eugenio Mercuri, M.D., Ph.D. and data for three historical control patients from the Leuven Neuromuscular Research Center were provided by Nathalie Goemans, M.D. The sponsor identified historical control patients who could be matched with subjects from Study 202 on specific characteristics including glucocorticoid use at baseline, sufficient longitudinal data for 6MWT, age ≥ 7 years, genotype amenable to any exon skipping therapy and genotype amenable to exon 51 skipping therapy. Functional assessments, including the 6MWT and NSAA, were performed as part of the clinical assessment of patients used as historical controls.

The sponsor evaluated the 6MWT comparing subjects from Study 202 to these historical controls over a 36 month time period. Both groups reportedly had decreases in 6MWT from baseline to 36 months. According to the sponsor, subjects in the eteplirsen group (Study 202) had a 6MWT = 263 meters compared to patients in the historical control group who had a

6MWT = 98.5 meters ($p = 0.009$) at 36 months. The sponsor reported that the mean change at 36 months was -100 meters in the eteplirsen group (Study 202) and -251 meters in the historical control group. Over the 36 month period, 6 patients in the historical control group lost the ability to ambulate (6MWT = 0) compared to 2 subjects in the eteplirsen group.

The focus of this assignment was to verify the data that the sponsor has submitted for the historical control group in Belgium. Specifically, for patients with 6MWT = 0, it was important to verify loss of ambulation (vs. refusal to cooperate) via review of any relevant and available source documents (e.g. progress notes, physical therapy, etc.). Additionally, verification of patient characteristics used to match to subjects in Study 202 was considered important (e.g. age, glucocorticoid use) as well as the type and frequency of physical therapy received.

This memo to file summarizes the information-gathering investigation of the three patients from the LNRC used as historical controls to compare to subjects enrolled in Study 202. The information gathering primarily included review of original hospital records with a focus on the 6MWT (primary functional efficacy endpoint) and other assessments included in hospital records. Information-gathering investigations for patients in the Italian DMD Telethon are pending.

III. Investigated Site and Results:

Name of Physician/Address	Number of Patients	Inspection Date
Nathalie Goemans, M.D. University Hospitals Leuven, Dept. of Child Neurology Herestraat 49 B-3000 Leuven, Belgium Nathalie.goemans@uzleuven.be	3	4/25/16 (one day)

Physician: Nathalie Goemans, M.D.; Belgium

Three patients from the Leuven Neuromuscular Reference Center were used as historical controls to compare to subjects enrolled in Study 202. Records reviewed included informed consent documents, genetic test results and electronic medical records. The electronic medical records included results of the 6MWT, 10 meter run/walk, rise time (rise from floor/Gower's) and climb four stairs assessments and the frequency of physical therapy. (b) (4)

(b) (4)

(b) (4). Dr. Goemans indicated that she did not have any other financial holdings in Sarepta Therapeutics, Inc.

For the 3 DMD patients, physiotherapists conducted the 6MWT, 10 meter walk/run, rise time, and climb four stairs assessments. The majority of the assessments were performed by one of the two physiotherapists. The physiotherapists were trained to conduct the 6MWT, rise from floor and 10 meter run assessments according to a standard protocol. Assessments were performed in the Physiotherapy Department. The 6MWT was performed during routine standard of care visits beginning in 2011/2012.

The 6MWT test area was marked with a 25-meter tape line starting at one cone extending to a second cone. As a safety measure, one assistant followed the patient during the assessment and the clinical evaluator documented the laps walked. The distance from one cone to the other was 25 meters or one lap. Positive verbal encouragement was given during the testing. According to Dr. Goemans, when the 6MWT assessments were first used, a score of 0 was recorded if the assessment was not completed in full. For 6MWT assessments that are currently performed, however, if the test is not completed, the total length walked is recorded.

Data Verification for Patient (b) (6)

(b) (6) was an (b) (6) male with DMD at the time the first 6MWT was performed on 6/18/2009.

- Genetic testing was performed by the University Hospital Leuven. The patient had deletion of exon 50 in the DMD gene which was verified.
- The 6MWT, 10 meter run/walk, rise time and NSAA scores in the data listings were compared to source documents. The data submitted for this patient included three visits in which the 6MWT = 0 while the 10 meter run/walk test was a recorded value (see Table 1). The 6MWT was given a score of 0 on two visits in which the patient was still ambulatory and able to complete the 10 meter run/walk, but could walk only short distances. In another visit, the 6MWT was given a score of 0 since the patient did not complete the entire six minute assessment though he was able to walk 125 meters during the assessment. The patient's non-ambulatory status was confirmed at the 9/29/2011 visit.

Table 1. Patient (b) (6): Dates of Visit, 6MWT, 10Meter Walk/Run Assessments and Reviewer Comments

Visit Date	6MWT (meters)	10 Meter Run/Walk (seconds)	Comments
6/18/2009	327	6.84	
1/14/2010	0	11.02	Patient remained ambulatory but only walks short distances and is afraid of falling
7/22/2010	0	10.85	Did not complete 6MWT; able to walk 125 meters in 3.28 minutes. After stopping, he no longer wanted to continue due to back pain.
3/10/2011	0	13.14	Patient was unable to walk 25 meters (distance between the two cones on 6MWT)
6/27/2011			Patient was evaluated for participation in a non-ambulatory DMD trial
9/29/2011	0	unable	Patient no longer able to walk and used an electric wheelchair Medical record "we still have not received any information to date regarding the study and continue to wait".

- Source documents indicated that the 10 meter run/walk was 6.46 seconds and the rise time was 20.40 seconds at the 2/26/2008 visit. In the data listing, there is no score listed for the 10 meter run/walk and the score for the rise time is 6.46.
- Source documents indicate the patient received deflazacort 6 mg from November 2005 through March 6, 2006 due to a misunderstanding in dosage by the patient's mother. The dose was later corrected to deflazacort 21 mg beginning March 7, 2006 and continuing.
- The field verified that data redacted from the 2/26/2008 source document was the patient's name.
- This patient was receiving physical therapy two to three times per week at school and once per week at home in 2010 and five times per week in 2011.

Data Verification for Patient (b) (6)

(b) (6) was an (b) (6) male with DMD at the time the first 6MWT was performed on 6/23/2009.

- Genetic testing was performed by the University Hospital Leuven. The patient had deletion of exon 52 in the DMD gene which was verified.

- The 6MWT, 10 meter run/walk, rise time, climb four stairs and NSAA scores in the data listings were verified with source documents. 6MWT results submitted for this patient were verified against source documents and are provided in Table 2. The inspection of source documents verified that the patient entered a clinical study after 9/19/2011 and was randomized to investigational drug. No further information regarding this clinical study is available. The 6MWT results after the patient was enrolled in the clinical study were 252, 240, and 50 meters. The inspection verified that the patient lost ambulation and become unable to perform the 10 meter run/walk at a visit on 12/13/2012 after he was enrolled in a clinical study.

Table 2. Patient (b) (6) Dates of Visit, 6MWT and Reviewer Comments

Visit Date	6MWT (meters)	Comments
6/23/2009	451	
10/13/2009	425	
4/27/2010	421	
10/26/2010	378	
5/5/2011	320	
9/19/2011	252	Patient entered a clinical study after 9/19/2011, randomized to investigational drug
3/6/2012	240	
7/30/2012	50	
12/13/2012	0	Verified loss of ambulation, still participating in a clinical trial
6/25/2013	0	

- The inspection verified that this patient began taking deflazacort 30 mg daily (rather than intermittently) in September 2008 as verified by medical records.
- This patient received daily physical therapy starting in 2010.

Data Verification for Patient (b) (6)

(b) (6) was an (b) (6) male with DMD at the time the first 6MWT was performed on 5/4/2010.

- Genetic testing was performed by the University Hospital Leuven. The patient had deletion of exons 45-50 in the DMD gene which was verified

- The 6MWT, 10 meter run/walk, rise time, climb four stairs, and NSAA scores in the data listings were verified with source documents. 6MWT results submitted for this patient and verified against source documents are provided in Table 3. The field noted that the patient began participation in the placebo arm of a clinical trial after the 5/16/2011 visit. No further information regarding this clinical study is available. This patient had a 6MWT = 0 at the 11/24/2014 visit and was unable to perform the 10 meter run/walk assessment. The field verified that, according to medical records, loss of ambulation occurred in 10/2014 and long leg braces were applied in 11/2014 to assist in standing.

Table 3. Patient ^{(b) (6)} Dates of Visit, 6MWT and Reviewer Comments

Visit Date	6MWT	Comments
5/4/2010	355	
9/9/2010	328	
5/16/2011	375	Patient participated in clinical trial after this visit; received placebo
8/8/2011	378	
1/24/2012	352	
4/16/2012	320	
12/13/2013	225	
11/24/2014	0	Loss of ambulation occurred in 10/2014, long leg braces were applied in 11/2014 to assist in standing

- This patient received physical therapy beginning in January 2006. The frequency of physical therapy was once per week at home in 2009.

The historical control data from the LNRC submitted by Sarepta Therapeutics in NDA 206488, specifically the 6MWT, 10 meter walk/run, rise time, and NSAA results were verified. The apparent discrepancies between the 6MWT and 10 meter walk/run results for patient BS were due to how the 6MWT was scored. For the 6MWT, patients who were unable to complete the entire 6 minute assessment were given a score of 0 (zero) and not the actual distance that they completed during this assessment. Patients who could not walk at least 25 meters (the distance between the two cones in the 6MWT) were also scored a 0. Therefore, for at least three assessments for patient BS, a 6MWT = 0 did not indicate inability to ambulate. For their analyses, the sponsor compared the 6MWT results from the historical control patients to the subjects in Study 202. If the patients were able to walk a specific distance, yet the value was recorded as 0 since the patient could not complete the entire 6MWT assessment, this could under estimate 6MWT results for the historical control patients. If distances are available for subjects not completing the entire 6MWT assessment, the division might wish to consider these data in their efficacy analyses.

DMD assessments are available for patient ^{(b) (6)} from 2009 until 2013, however, this patient entered a clinical study in 2011 and was randomized to investigational drug. This patient lost

his ability to ambulate in 2012, while receiving investigational drug. The division should consider whether any DMD assessments after the date the patient enrolled in this clinical trial should be considered part of the natural history course for this patient.

DMD assessments were available for patient ^{(b) (6)} from 2010 until 2014, however, this patient entered a clinical study in 2011. Though this patient received placebo during this clinical study, participation in a study may impact the natural history course for this patient (e.g. motivation of patient/staff, etc.). The division should consider whether any DMD assessments after the date the patient enrolled in this clinical trial should be considered part of the natural history course for this patient.

CC:

Central Document Room/NDA 206488
DNP /Division Director/Billy Dunn
DNP/Deputy Division Director/Eric Bastings
DNP /Medical Team Leader/Ronald Farkas
DNP Medical Officer/Christopher Breder
DNP /Project Manager/Fannie Choy
OSI/Office Director (Acting)/David Burrow
OSI/DCCE/ Division Director/Ni Khin
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OSI/DCCE/Team Leader/Susan Thompson
OSI/DCCE/GCPAB Reviewer/Cara Alfaro
OSI/ GCPAB Program Analysts/Joseph Peacock/Yolanda Patague
OSI/Database Project Manager/Dana Walters

{ See appended electronic signature page }

Cara Alfaro
Clinical Analyst
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{ See appended electronic signature page }

Susan Thompson, M.D.
Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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/s/

CARA L ALFARO

05/23/2016

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SUSAN D THOMPSON

05/24/2016

KASSA AYALEW

05/24/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: April 28, 2016
Requesting Office or Division: Division of Neurology Products (DNP)
Application Type and Number: NDA 206488
Product Name and Strength: Exondys 51 (eteplirsen) Injection, 50 mg/mL
Submission Date: March 28, 2016
Applicant/Sponsor Name: Sarepta Therapeutics, Inc.
OSE RCM #: 2015-1123-2
DMEPA Primary Reviewer: Justine Harris, RPh
DMEPA Team Leader: Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Neurology Products (DNP) requested that we review the revised container labels and carton labeling for Exondys 51 (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSION

The revised container labels and carton labeling for Exondys 51 is acceptable from a medication error perspective. We have no further recommendations at this time.

¹ Myers, D. Label and Labeling Review MEMO for EXONDYS 51 (NDA 206488). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 JAN 11. 5 p. OSE RCM No.: 2015-1123-1.

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/s/

JUSTINE HARRIS
04/28/2016

DANIELLE M HARRIS
04/28/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: January 11, 2016
Requesting Office or Division: Division of Neurology Products (DNP)
Application Type and Number: NDA 206488
Product Name and Strength: Exondys 51 (eteplirsen) Injection, 50 mg/mL
Submission Date: December 17, 2015
Applicant/Sponsor Name: Sarepta Therapeutics, Inc.
OSE RCM #: 2015-1123-1
DMEPA Primary Reviewer: Deborah Myers, RPh, MBA
DMEPA Team Leader: Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Neurology Products (DNP) requested that we review the revised container labels and carton labeling for Exondys 51 (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSION

The revised container labels and carton labeling are unacceptable from a medication error perspective because both the lot number and expiration dates are no longer included. Additionally, the storage statement can be revised to increase clarity.

¹ Myers, D. Label and Labeling Review for Exondys 51 (NDA 206488). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 OCT 23. 9 p. OSE RCM No.:2015-1123.

3 RECOMMENDATIONS FOR SAREPTA THERAPEUTICS, INC.

We recommend the following be implemented prior to approval of this NDA:

All Container Labels and Carton Labeling

1. We note that your updated container labels and carton labeling no longer includes space notated for the product lot and expiration date. Please add this information to both the container labels and carton labeling.

All Carton Labeling

2. We note that as requested you bolded the storage statement on the carton labeling. However, the statement as currently displayed "**Refrigerate at 2-8 °C (36-46 °F)**" is missing the degree and centigrade symbols (°C) after the numbers 2 and 36, and includes an extra space between the numbers 8 and 46 and their degree symbol. Please revise this bolded statement to read "**Refrigerate at 2°C-8°C (36°C-46°F).**"

10 mL Container Labels

3. Revise the Storage statements on the 10 mL container label, by inserting the degree and centigrade symbols (°C) after the numbers 2 and 36, to read "**Refrigerate at 2°C-8°C (36°C-46°F).**"

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

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/s/

DEBORAH E MYERS
01/11/2016

DANIELLE M HARRIS
01/11/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: October 23, 2015
Requesting Office or Division: Division of Neurology Products (DNP)
Application Type and Number: NDA 206488
Product Name and Strength: Exondys 51 (eteplirsen) Injection, 50 mg/mL
Product Type: Single-Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Sarepta Therapeutics, Inc.
Submission Date: June 26, 2015
OSE RCM #: 2015-1123
DMEPA Primary Reviewer: Deborah Myers, RPh, MBA
DMEPA Team Leader: Danielle Harris, PharmD, BCPS

1 REASON FOR REVIEW

This review is written in response to a request from the Division of Neurology Products (DNP) to review the proposed labels and labeling for Exondys 51 (eteplirsen) injection [NDA 206488] for vulnerabilities to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	N/A
ISMP Newsletters	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the proposed labels and labeling identified areas that can be improved to increase clarity, improve readability, and increase prominence of important information to minimize the risk of medication errors and promote the safe use of Exondys 51.

Our review noted that the dosage form, injection, is missing from the Prescribing Information, Section 16, *How Supplied/Storage and Handling*. This information is required for inclusion per 21 CFR 201.57(c)(17).

We also noted that the National Drug Code (NDC) numbers for both the 2 mL and 10 mL vials have the same product code (middle digits of the NDC number), -051. While these two products do share the same strength/concentration of 50 mg/mL, they contain different total amount of drug in the container because of differences in fill volumes (i.e., 100 mg vs. 500 mg). When the same product code number is used for different sized containers, we have experience in which healthcare providers have had difficulty distinguishing the difference in total drug content, which has led to wrong dose medication errors.

Our review of the carton labeling identified the following concerns:

- The NDC number is located on the side panel of the carton labeling. Since the NDC number is often used as an additional verification method in the pharmacy, it is an important safety feature that should be displayed on the principle display panel (PDP).
- The Rx Only statement is currently presented on the side panel of the carton labeling, whereas it is traditionally positioned on the PDP to ensure its prominence.
- The net quantity statement is missing from and needs to be added to the carton PDP in accordance with 21 CFR 201.51.
- The storage statement lacks prominence and could be revised to minimize the risk of storage information from being overlooked.

Our review of the container labels determined that all critical information is present. We note that the statements of strength are not differentiated by means of color or boxing, however, we find this acceptable as the vials are of different size, which we believe will provide adequate differentiation. Additionally, the vials are packaged within cartons that have adequate differentiation of strength. Thus, apart from our comments above regarding the NDC product code, we have no additional recommendations for the labels from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

We identified areas of the label and labeling that can be revised to increase clarity, improve readability, and add important critical information to mitigate the potential for medication errors. We provide recommendations in Sections 4.1 and 4.2 below and advise they are implemented prior to the approval of this NDA.

4.1 RECOMMENDATIONS FOR THE DIVISION

- A. Full Prescribing Information, Section 16, *How Supplied/Storage and Handling*
1. The dosage form for this product is not included. 21 CFR 201.57(c)(17) states, in Section 16 *How Supplied/Storage and Handling* this section must contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible. Thus, we request the dosage form, injection, be added to this Section following the product name, EXONDYS 51.
 2. We recommend the middle digits (“-051-”) of the NDC (i.e.; the “product code”) for the 2 mL and 10 mL vials be revised so that they are not identical. Although the vials contain the same product concentration, they contain different total amount of drug in the container because of differences in the fill volume. When the same product code number is used for different size containers, healthcare providers have had difficulty distinguishing the difference in total drug content. Therefore, we

recommend a unique product code be used for each vial to help differentiate between these products and prevent wrong dose medication errors.

4.2 RECOMMENDATIONS FOR SAREPTA THERAPEUTICS, INC.

We recommend the following be implemented prior to approval of this NDA 206488:

A. Carton Labeling

1. As currently presented, the NDC number is located on the side panel of the carton labeling. Since NDC number is often used as an additional verification method in the pharmacy, it is an important safety feature. Relocate the NDC so that it is displayed in the top third of principal display panel (PDP) of the labeling in accordance with 21 CFR 207.35(3)(i).
2. The “Rx Only” statement is currently presented on the side panel of the carton labeling; consider relocating this statement to the PDP.
3. Revise the middle digits (“-051-”) of the NDC (i.e.; the “product code”) for the 2 mL and 10 mL vials so that they are not identical. Although the vials contain the same product concentration, they contain different total amount of drug in the container because of differences in the fill volume. When the same product code number is used for different size containers, healthcare providers have had difficulty distinguishing the difference in total drug content. Therefore, revise the product code (middle digits of the NDC number) such that they are different between these products to prevent wrong dose medication errors. See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013.*
4. Add the net quantity statement (i.e., 1 vial) to the carton PDP in accordance with 21 CFR 201.51. Ensure that the net quantity statement appears away from the product strength and is less prominent.
5. Revise and bold the statement “(b) (4) **2°C-8°C (36°C-46°F).**” We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked.

B. Container Labels

1. See A.3. above.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Exondys 51 that Sarepta Therapeutics, Inc. submitted on June 26, 2015.

Table 2. Relevant Product Information for Exondys 51	
Initial Approval Date	N/A
Active Ingredient	eteplirsen
Indication	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. (b) (4) <div style="background-color: #cccccc; height: 15px; width: 100%;"></div> <div style="background-color: #cccccc; height: 15px; width: 100%;"></div> <div style="background-color: #cccccc; height: 15px; width: 100%;"></div>
Route of Administration	Intravenous (IV) Infusion
Dosage Form	Injection, concentrated solution for dilution
Strength	100 mg (50 mg/mL) and 500 mg (50 mg/mL)
Dose and Frequency	30 mg/kg administered once-weekly as an intravenous infusions between 35 to 60 minutes in duration.
How Supplied	Single-use; 2 mL vials containing 100 mg (50 mg/mL) and 10 mL vials containing 500 mg (50 mg/mL)
Storage	Store at 2°C to 8°C (36° to 46°F). Do not freeze. Protect from light and store in the original carton until ready for use.
Container Closure	(b) (4) <div style="background-color: #cccccc; height: 20px; width: 100%;"></div>

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On October 22, 2015, we searched the L:drive and AIMS using the term, eteplirsen to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified three previous reviews, and we confirmed that our three previous reviews contain no outstanding recommendations.¹²³

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¹ Harris, J. Proprietary Name Memorandum for Exondys 51 NDA 206488. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 SEP 30. RCM No.: 2015-1341038.

² Harris, J. Proprietary Name Review for Exondys 51IND 077429. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 OCT 29. RCM No.: 2014-25473.

³ Liu, S. Proprietary Name Memorandum for Aclivate IND 077429. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 AUG 16. RCM No.: 2013-532.

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/s/

DEBORAH E MYERS
10/23/2015

DANIELLE M HARRIS
10/23/2015



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: November 23, 2015

To: Billy Dunn, M.D., Director
Division of Neurology Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Martin S. Rusinowitz, M.D., Medical Officer
Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: EXONDYS 51 (eteplirsen injection)
NDA 206,488
Indication: Treatment of Duchenne Muscular Dystrophy
Dosage: 30 mg/kg intravenously once-weekly
Sponsor: Sarepta Therapeutics, Inc.

Materials reviewed: Sponsor's Nonclinical and Clinical Summaries (June 26, 2015)

Background

The Division of Neurology Products (DNP) consulted the Controlled Substance Staff (CSS) regarding an assessment of abuse potential for eteplirsen under NDA 206,488. Eteplirsen is indicated for the treatment of Duchenne Muscular Dystrophy (DMD), a degenerative X-linked recessive genetic neuromuscular disease caused by mutations in the DMD gene that encodes dystrophin.

DMD affects approximately 1 in 3,500 newborn males worldwide and approximately 15,000 patients in the United States. This rare, progressively debilitating, and ultimately fatal neuromuscular disorder affects dystrophin, a critically important part of the dystrophin-associated protein complex that connects the cytoskeletal actin of a muscle fiber to the extracellular matrix. In the absence of dystrophin, the stress of repeated muscle contractions damages the membrane around the individual muscle cell, resulting in repeated cycles of cellular degeneration, regeneration and inflammation. Over time, the

inherent ability of muscle cells to repair and regenerate is exhausted and muscle is replaced by fibrotic tissue and fat.

The Sponsor states that eteplirsen is an exon-skipping phosphorodiamidate morpholino oligomer that restores the mRNA reading frame to produce dystrophin protein. Thus, EXONDYS 51 (eteplirsen injection) is indicated for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

(b) (4)

Conclusions and Recommendations

1. After a review of the summary materials in NDA 206,488, CSS concludes that eteplirsen does not have the profile of a drug with abuse potential because it:
 - Does not produce central nervous system behaviors in either animals or humans
 - Has a mechanism of action that is limited to effects on mRNA
 - Does not distribute into the brain after intravenous administration
2. Thus, CSS concludes that an abuse potential assessment for eteplirsen is unnecessary.

Discussion

The nonclinical and clinical summaries in the NDA do not provide any indication that eteplirsen has central nervous system activity.

The nonclinical summary states that the Sponsor did not conduct abuse-related studies, given that eteplirsen:

- Has a mechanism of action that is limited to effects on mRNA.
- Does not distribute into the brain after intravenous administration, as demonstrated by mouse quantitative whole body autoradiography showing that levels of drug were not detectable in the brain.
- Does not produce central nervous system behaviors in a safety pharmacology study in monkeys, as demonstrated by a lack of changes in neurological function (including level of consciousness, motor function, and eye movements) in rats and monkeys following administration of eteplirsen at the highest dose tested (320 mg/kg).

Clinically, the most common treatment emergent adverse events (TEAEs) occurring more frequently in patients treated with eteplirsen 30 or 50 mg/kg IV than in patients treated with placebo were headache, arthralgia, vomiting, nausea, upper respiratory tract infection, nasopharyngitis, cough, and procedural pain. However, these types of AEs may

be related to upper respiratory infections or joint pain associated with the disease and are often reported in the pediatric population with Duchenne Muscular Dystrophy. Thus, the reported AEs may not be in response to eteplirsen.

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/s/

MARTIN S RUSINOWITZ
11/23/2015

KATHERINE R BONSON
11/23/2015

MICHAEL KLEIN
11/24/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # NDA 206488 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: EXONDYS 51 Established/Proper Name: Eteplirsen Dosage Form: Injection Strengths: 50 mg/mL		
Applicant: Sarepta Therapeutics, Inc. Agent for Applicant (if applicable):		
Date of Application: June 26, 2015 Date of Receipt: June 26, 2015 Date clock started after UN:		
PDUFA/BsUFA Goal Date: Feb 26, 2016		Action Goal Date (if different):
Filing Date: August 25, 2015		Date of Filing Meeting: August 4, 2015
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
The application will be a priority review if:	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"> • <i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i> • <i>The product is a Qualified Infectious Disease Product (QIDP)</i> • <i>A Tropical Disease Priority Review Voucher was submitted</i> • <i>A Pediatric Rare Disease Priority Review Voucher was submitted</i> 	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults	

<input checked="" type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input checked="" type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product): N/A

List referenced IND Number(s): **IND 077429**

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		9/3/15: request DR staff to update established name for the supporting IND

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.			√	
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>	√	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov:</i>)			
	<input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees:			
	<input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i>			
	N/A <input type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

cover letter, and annotated labeling). If yes , answer the bulleted questions below:							
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				<input type="checkbox"/>	<input type="checkbox"/>	√	
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].				<input type="checkbox"/>	<input type="checkbox"/>	√	
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?				<input type="checkbox"/>	<input type="checkbox"/>	√	
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>							
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?				<input type="checkbox"/>	<input type="checkbox"/>	√	
Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm							
If yes , please list below:							
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration				
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>							
Exclusivity	YES	NO	NA	Comment			
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>					
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>				
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>							
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>				
If yes , # years requested: 5 years							
Note: An applicant can receive exclusivity without requesting it;							

<i>therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input checked="" type="checkbox"/> Mixed (CTD/non-CTD) non-CTD submission contains dystrophin images requested by the Agency. DNP consulted eSUB for technical advice for the non-CTD/physical media submission.			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	N/A			
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>		On 8/11/15, the

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

(NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible - yes <input checked="" type="checkbox"/> English (or translated into English) - yes <input checked="" type="checkbox"/> pagination - yes <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) - no If no, explain.				Division met with the Applicant and discussed deficient Define files and hyperlinking. The Applicant has promised to replace or repair this material in a timely manner.
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>				
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff: 7/28/15</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<p>NME: CSS consult sent on 7/28/15.</p> <p>Abuse Liability assessment was not included in the application.</p>
Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Orphan designation, exempt from PREA

²

<i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<u>BPCA:</u> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Proprietary Name /Request for review submitted on 8/28/15.
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

³

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format? ⁵	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Applicant submitted PI in PLLR format.
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult: 8/25/15 Pt Labeling team not consulted: no PPI, IFU or MedGuide.
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	OSE/DRISK attended Filing Meeting
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	OSE/DMEPA and OPQ attended Filing Meeting
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Are annotated specifications submitted for all stock keeping	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	None identified at the Filing Meeting. The team discussed that OSIS consult is not needed because an inspection of the clinical lab at NCH was conducted on 5/29-5/30/2014.
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 3/13/13 EOP2, 7/23/13 follow-up to EOP2 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 9/3/14 CMC presubmission; 9/18/14 pre-NDA Mtg #1, 5/15/15 pre-NDA Meeting #2 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 4, 2015

BACKGROUND: NDA 206488
EXONDYS 51 (eteplirsen) injection for intravenous infusion 50 mg/mL

The sponsor submitted this original new drug application (NDA) for eteplirsen 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. Eteplirsen was developed under IND 077429. Eteplirsen is a phosphorodiamidate morpholino oligomer (PMO). Its putative mechanism of action is to selectively bind to exon 51 of dystrophin pre-mRNA.

The Agency granted orphan drug designation and fast track designation for eteplirsen for the treatment of DMD on October 23, 2007, and November 27, 2007, respectively.

On March 13, 2013, an end-of-phase 2 (EOP2) meeting was held between the Agency and the sponsor. The sponsor had requested the Agency's opinion on the suitability of filing a New Drug Application (NDA) for eteplirsen to treat DMD. On July 23, 2013, a Type C meeting was held as a follow-up to the EOP2 meeting, to continue discussion regarding the acceptability of the proposed NDA filing. Issues requiring further discussion from the Type C meeting were for the sponsor to generate additional data to support filing, and to start a controlled trial as soon as possible with the newly manufactured drug.

The Agency and the sponsor held follow-up meetings on November 8, 2013, November 15, 2013, December 19, 2013 and March 19, 2014. The purpose of the meetings was to discuss the evidence supporting the efficacy of eteplirsen for the treatment of DMD, and the design of future studies.

On April 15, 2014, the Agency provided the sponsor with a guidance letter describing FDA's view of the clinical and biomarker data currently available for eteplirsen and proposed a strategy for the sponsor to consider regarding the submission of an NDA for eteplirsen.

CMC pre-submission meeting was held on September 3, 2014. Pre-NDA meetings were held on September 18, 2014, and May 15, 2015, to agree on data that would constitute a complete NDA.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Fannie (Yuet) Choy	Y
	CPMS/TL:	Jacqueline Ware	Y

Cross-Discipline Team Leader (CDTL)	Ron Farkas		Y
Division Director/Deputy	Billy Dunn / Eric Bastings		Y / Y
Office Director/Deputy	Ellis Unger / Robert Temple		Y / Y
Clinical	Reviewer:	Chris Breder	Y
	TL:	Ron Farkas	Y
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:		
Clinical Pharmacology	Reviewer:	Ta-Chen Wu (PK) Atul Bhattaram (PM) Hobart Rogers (Genomics)	Y Y Y
	TL:	Angela Men (PK) Kevin Krudys (PM) Christian Grimstein (Genomics)	N Y N
Biostatistics	Reviewer:	Xiang Ling	Y
	TL:	Kun Jin	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Dave Hawver	N
	TL:	Lois Freed	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:		
Product Quality (CMC) Review Team:	ATL:	Martha Heimann	Y
	RBPM:	Dahlia Woody	Y
• Drug Substance	Reviewer:	Joseph Leginus	N
• Drug Product	Reviewer:	Mari Chelliah	N
• Process	Reviewer:	Sung Kim	N
• Microbiology	Reviewer:	Denise Miller	N
• Facility	Reviewer:	Zhong Li	N
• Biopharmaceutics	Reviewer:	N/A	
• Immunogenicity	Reviewer:	N/A	
• Labeling (BLAs only)	Reviewer:	N/A	
• Other (e.g., Branch Chiefs, EA Reviewer)	N/A		
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	N/A	

	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Aline Moukhtara	N
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Deborah Myers	Y
	TL:	Danielle Harris	N
OSE/DRISK (REMS)	Reviewer:	Robert Pratt	Y
	TL:	Jamie Wilkins Parker	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	Tony El Hage	Y
	TL:	Susan Thompson	N
Controlled Substance Staff (CSS)	Reviewer:	Katherine Bonson	N
	TL:	Michael Klein	N
Other reviewers/disciplines			
OBP/ Bioassay	Reviewer:	Ashutosh Rao	Y
	TL:		
DACCM (Advisory Committee)	DFO:	Phil Bautista	Y
	TL:	Deim Ngo	N
Other attendees	OSE PM:	Ermias Zerislassie	Y
	Nonclinical:	Barbara Wilcox	Y
	RPM:	Laurie Kelley	Y
	Rare Diseases:	Kathy O'Connell	Y
	Clinical:	Veneeta Tandon	Y
	Clinical TL:	Nick Kozauer	Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments: Refer to the communication sent to sponsor and filed in DARRTS on 8/6/15. On 8/11/15, the Division met with the Applicant and discussed deficient Define files and hyperlinking. The Applicant has promised to replace or repair this material in a timely manner.</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> No comments
<p>CLINICAL</p> <p>Comments: Refer to Clinical initial overview of application for filing in DARRTS (8/25/15).</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain: There was a discussion that an inspection was performed between Dec 2 and 5, 2013 at the clinical site (Nationwide Children’s Hospital) for studies 201 and 202.</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p>	<input checked="" type="checkbox"/> YES Date if known: <input type="text"/> <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined

<p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<p>Planned for 2nd week of Jan 2016.</p> <p>Reason:</p>
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments: Request for CSS consult sent (NME)</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u>	
<ul style="list-style-type: none"> Is the product an NME? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<u>Environmental Assessment</u>	
<ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
<u>Facility Inspection</u>	<input type="checkbox"/> Not Applicable
<ul style="list-style-type: none"> Establishment(s) ready for inspection? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
<u>Facility/Microbiology Review (BLAs only)</u>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
<u>CMC Labeling Review (BLAs only)</u>	N/A
Comments:	<input type="checkbox"/> Review issues for 74-day letter

<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO N/A
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	NO
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Ellis Unger, M.D., ODE1 Director

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 10/13/15

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

During the Filing Meeting, various disciplines (Clinical, Bioassay, Biostatistics, Clinical Pharmacology, Pharmacometrics) have identified potential navigation issues, outstanding data and information. The Division communicated comments and information requests to the firm on 8/6/15 (communication filed in DARRTS). On 8/11/15, the Division held a teleconference with the firm and discussed deficient Define files and hyperlinking. The firm committed to replace or repair the material in a timely manner. During the teleconference, the firm also committed to provide the overlay images indicating what muscle fibers were considered dystrophin+ by the individuals counting these fibers (8/11/15 information request filed in DARRTS). The firm has subsequently submitted the requested information on August 20 and 28, 2015, and noted its commitment to submit the marked immunohistochemistry images as soon as it can (around October 11, 2015).

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review</p>

ACTION ITEMS

<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

<input checked="" type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

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
09/08/2015

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 206488

Application Type: New NDA (NME)

Name of Drug/Dosage Form: EXONDYS 51 (eteplirsen) injection, for intravenous use

Applicant: Sarepta Therapeutics, Inc.

Receipt Date: June 26, 2015

Goal Date: February 26, 2016

1. Regulatory History and Applicant's Main Proposals

The sponsor submitted this original new drug application (NDA 206488) for eteplirsen 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. Eteplirsen is a phosphorodiamidate morpholino oligomer (PMO). It was being developed under IND 077429.

The Agency granted orphan drug designation and fast track designation for eteplirsen for the treatment of DMD on October 23, 2007, and November 27, 2007, respectively.

The Agency held multiple meetings with the sponsor to discuss the evidence supporting the efficacy of eteplirsen for the treatment of DMD, and the design of studies. On April 15, 2014, the Agency provided the sponsor with a guidance letter describing FDA's view of the clinical and biomarker data available for eteplirsen and proposed a strategy to consider regarding the submission of an NDA for eteplirsen.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

The following labeling issues were identified:

General

- Remove all page numbers throughout the labeling.

RPM PLR Format Review of the Prescribing Information

Table of Contents

- The statement “*Sections or subsections omitted from the full prescribing information are not listed” should not be bolded.

All SRPI format deficiencies of the PI (if any) and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by September 29, 2015. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required

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• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

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Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

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Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

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Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

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Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *The proposed PI follows the format requirements for subsections of 8.1 through 8.3 of the “Pregnancy and Lactation Labeling Rule” (PLLR).*

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed

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within brackets. For example, “[see Warnings and Precautions (5.2)]” or “[see Warnings and Precautions (5.2)]”.

Comment:

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the 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.”

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

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PATIENT COUNSELING INFORMATION Section in the FPI

- N/A** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- N/A** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

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Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]

Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)]

[m/year]

[section (X.X)]

[m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

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/s/

YUET L CHOY
09/04/2015