

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206488Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW

Date: May 3, 2016

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Subject: Evaluation to determine if a REMS is necessary

Drug Name(s): Eteplirsen (Exondys 51)

Therapeutic Class: Antisense oligonucleotide

Dosage and Route: 30 mg/kg administered by intravenous infusion once-weekly

Indication: Treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene amenable to exon 51 skipping therapy

Application Type/Number: NDA 206488

Applicant: Sarepta Therapeutics, Inc.

OSE RCM #: 2015-1122

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) is needed for the new molecular entity (NME) eteplirsen injection, NDA 206488. Sarepta Therapeutics, Inc. (Sarepta) completed submission of a rolling NDA application on June 26, 2015, with the proposed indication to treat Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene amenable to exon 51 skipping therapy. Sarepta did not submit a proposed REMS or risk management plan with their application.

1.1 DISEASE BACKGROUND

DMD is a rare, severe, incurable, X-linked recessive, neuromuscular genetic disease caused by various mutations in the gene encoding dystrophin, a protein critical to the structural stability of myofibers in skeletal and cardiac muscle. The vast majority of the mutations are deletions, including deletions around exon 51 of the gene, which terminate dystrophin synthesis. The absence of dystrophin results in muscle degeneration that progresses through childhood and adolescence with eventual loss of ambulation and wheelchair dependence, decreased respiratory function and ventilator dependence, cardiomyopathy, and death. Patients often die in their late teens to twenties.¹⁻² DMD occurs almost exclusively in males and has a U.S. prevalence of approximately 18,000 individuals. In the NDA Clinical Overview, the applicant estimates 2,000 of these individuals have a mutation amenable to skipping exon 51 of the dystrophin gene.

There are no approved treatments for DMD. Glucocorticoid therapy is the mainstay of treatment and associated with an increase in strength, muscle function, and pulmonary function, though the duration of benefit is uncertain. The risks associated with treatment of corticosteroids in patients with DMD include behavioral changes and Cushingoid appearance, as well as the potential for adverse effects associated with long-term therapy, such as bone fractures, cataracts, delayed puberty, growth failure with short stature, and other risks.^{2,3}

1.2 PRODUCT BACKGROUND

Eteplirsen is an antisense oligonucleotide with a sequence designed to mask and induce the skipping of exon 51 from the dystrophin pre-mRNA during the splicing process. This might restore the mRNA reading frame for translation and enable production of an internally truncated, semi-functional dystrophin protein. By increasing the quantity of abnormal, but potentially functional dystrophin, the objective is to slow or prevent the progression of DMD. The proposed dose of eteplirsen is administration of 30 mg/kg once-weekly by intravenous infusion.

1.3 REGULATORY HISTORY

The following is a summary of the regulatory history relevant to the evaluation of whether a REMS for eteplirsen is necessary to ensure the benefits outweigh the any risks:

October 23, 2007: Eteplirsen received Orphan Product Designation for the treatment of Duchenne muscular dystrophy.

¹ Darras BT. Clinical features and diagnosis of Duchenne and Becker muscular dystrophy. In:UpToDate, Patterson MC, Firth HV, Dashe JF (Eds), UpToDate, Waltham, MA, 2015.

² McNeil, DE, et al. Duchenne muscular dystrophy: drug development and regulatory considerations. Muscle Nerve 2010; 41:740-745.

June 26, 2015: The final portion of a rolling original NDA was received for eteplirsen (NDA 206488). The applicant did not submit a proposed REMS or risk management plan.

August 20, 2015: The Priority Review Determination letter stated the application is sufficiently complete to permit a substantive review, which was classified as Priority.

October 22, 2015: The mid-cycle communication meeting agenda stated there is currently no plan for a REMS; during the teleconference with the applicant, there was no discussion related to the need for a REMS.

December 23, 2015: The late-cycle meeting background package stated no issues related to risk management have been identified to date.

February 5, 2016: A Review Extension Major Amendment letter was sent to the applicant.

April 25, 2016: The application was discussed by the Peripheral and Central Nervous System Drugs Advisory Committee.

2 MATERIALS REVIEWED

The following is a list of materials used to inform this review:

- Sarepta Therapeutics, Inc. Eteplirsen, NDA 206488 submission, received June 26, 2015 (Serial No. 1)
 - Section 2.5, Clinical Overview
 - Section 2.7.4, Summary of Clinical Safety
- Division of Neurology Products (DNP). Mid-Cycle meeting #1 slides, NDA 206488, October 13, 2015
- Division of Neurology Products. Mid-Cycle meeting #2 slides, NDA 206488, October 19, 2015
- Division of Neurology Products, Draft Prescribing Information, NDA 206488, November 8, 2015
- Division of Neurology Products. Mid-Cycle Communication Meeting Minutes, NDA 206488, November 20, 2015
- Breder, C., Division of Neurology Products, Draft Clinical Review, NDA 206488, dated December 4, 2015
- FDA Briefing Document, Peripheral and Central Nervous System Drugs Advisory Committee Meeting, dated April 9, 2016

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM

Efficacy and safety of eteplirsen were evaluated in a single-center, randomized, double-blind, placebo-controlled, crossover study (Study 201) of eteplirsen (30 or 50 mg/kg/week) in 12 ambulatory boys with DMD mutations amenable to exon 51 skipping. Patients who completed Study 201 continued treatment in an ongoing, open-label extension (described as Study 202) of eteplirsen 30 or 50 mg/kg/week. The multidisciplinary review team's analysis of the applicant's submission is described below.

3.2 SUMMARY OF EFFICACY

The primary efficacy endpoint in Study 201 was the change from baseline in the percentage of dystrophin-positive fibers in muscle biopsy tissue at Week 12 for the 50 mg/kg group and Week 24 for the 30 mg/kg group. Several secondary efficacy endpoints were also assessed, including functional assessments such as the 6-minute walk test (6MWT); the Timed Four Step Test; the North Star Ambulatory Assessment (NSAA), which is a clinician-reported outcome instrument that measures ambulatory function; and the testing of Rise Time (time to rise from lying supine on the floor to standing), among other tests. The primary endpoints in Study 202 were the change from baseline in 6MWT over time and the change from baseline in the percentage of dystrophin-positive fibers in muscle biopsy tissue at Week 48 (with reference to enrollment in Study 201). Secondary efficacy endpoints were also assessed. The statistical reviewer noted that no multiplicity adjustment was specified for testing multiple doses and/or multiple endpoints, so all p-values are considered exploratory only.

Using immunofluorescence analysis, the applicant reported that patients treated with 30 mg/kg/week eteplirsen demonstrated an increase in the mean percentage of dystrophin-positive fibers from a baseline of 18% to 41% of normal ($p \leq 0.002$) at Week 24. (A re-analysis of these results by a blinded panel found an increase from a baseline of 14% to 27% at Week 24.) There was essentially no mean increase from baseline (11% to 11.8%) in patients treated with 50 mg/kg/week ($p=0.958$) at Week 12. Patients who crossed over from placebo to either the 30 mg/kg or 50 mg/kg treatment schedule during the open-label extension did not increase the percentage of positive fibers by Week 48. Of note, the clinical reviewer found a number of deficiencies in the quantitative methodology, as well as a high degree of inter-rater variability in quantifying fiber counts. Moreover, Western blot analysis did not confirm the results reported using immunofluorescence; Western blot estimated the mean dystrophin level after approximately 3.5 years of treatment to be $0.9\% \pm 0.8\%$ of normal (whereas the proportion of muscle fibers with detectable dystrophin identified by immunofluorescence was $17\% \pm 10\%$ of normal).

The adjusted mean change from baseline in 6MWT scores (using ranked data) found no difference in distance between the eteplirsen groups (6.6 m) and the placebo group (6.4 m) at Week 24 ($p=0.94$). The applicant asserted that a comparison of the eteplirsen-treated patients with natural history controls over time showed an improved clinical course; however, the review team has uncertainty over the interpretability of the comparison and whether the differences were due to eteplirsen or other factors, such as differences in physical therapy, corticosteroid regimens, selection of patients, or other factors.

With regard to the secondary trial endpoints, the mean time required to complete the Four Step Test at Week 24 decreased slightly from baseline in the placebo (-1.22 sec) and 50 mg/kg (-0.15 sec) groups, whereas the time increased (+9.85 sec) in the 30 mg/kg group.

The North Star Ambulatory Assessment (NSAA) is a clinician-reported outcome instrument that measures ambulatory function in patients with DMD. Assessment of the change in NSAA mean scores from baseline showed a numerical difference at Week 24 in favor of eteplirsen 50 mg/kg compared with placebo ($p=0.06$) but a difference in favor of placebo ($p=0.38$) compared with the eteplirsen 30 mg/kg group.

The change in rise time (time to rise from lying supine on the floor to standing) from baseline found no differences between the groups. The 30 mg/kg (5.7 sec) and 50 mg/kg (4.6 sec) groups were numerically worse than the placebo group (-0.7 sec) through Week 24.

3.3 SUMMARY OF SAFETY

For the purpose of this review, serious adverse events (SAEs) are defined by the regulatory definition of a serious outcome, such as death, a life-threatening reaction, or hospitalization, among other outcomes. Severe adverse events (AEs) were categorized as such by the clinical investigator. The safety population included data on a total of 114 patients who were exposed to eteplirsen in seven completed or ongoing clinical studies. Of these patients, 46 were treated with eteplirsen doses of 30 mg/kg or greater.

3.3.1 Deaths

No patients have died during the eteplirsen clinical development program.

3.3.2 Nonfatal serious adverse events

Nonfatal SAEs were reported in six patients in the safety population. The SAEs included wound infection, vomiting, ankle fracture, femur fracture, oxygen saturation decreased, and viral lymphadenitis. These events were considered by the clinical reviewer as unrelated to treatment, though a causal relationship could not be excluded.

3.3.3 Severe adverse events

Nine adverse events occurring in six patients were assessed as severe. The events included incision site hemorrhage, hemorrhoids, back pain, nasal congestion, bone pain, loss of balance, viral lymphadenitis, femur fracture, and cardiomyopathy with left ventricular dysfunction. All of the events were judged by the investigator to be unrelated except for cardiomyopathy, which was considered possibly related; a review of echocardiograms for this patient, a 10 year-old boy, showed he had pre-existing cardiomyopathy. The boy discontinued treatment due to a decrease in left ventricular ejection fraction after having received seven once-weekly doses of eteplirsen 4 mg/kg.

3.3.4 Common adverse reactions

The most common adverse reactions reported in $\geq 10\%$ of patients (n=46) treated with eteplirsen ≥ 30 mg/kg that occurred more frequently than in patients treated with placebo were headache, vomiting, cough, upper respiratory tract infection, arthralgia, nasopharyngitis, and nausea. The majority of these events were mild and resolved during continued treatment.

4 DISCUSSION

Duchenne muscular dystrophy is a rare, lethal, genetic disease that is without any approved therapeutic options. Treatment with antisense oligonucleotides, such as eteplirsen, intend to induce specific exon skipping during mRNA splicing to correct an open reading frame of the dystrophin gene and restore dystrophin expression. The multidisciplinary review team has concerns regarding the strength of evidence provided to support this drug's efficacy for the treatment of DMD in patients with a gene mutation amenable to exon 51 skipping therapy.

Although the overall incidence of serious or severe adverse events is low, the clinical reviewer's perspective is that the small safety database makes it difficult to fully characterize the drug's adverse event profile. In addition, the Agency's advisory committee briefing document notes

most of the exposures to eteplirsen were outside of placebo-controlled studies, limiting the ability to determine if adverse events were the result of drug effect or chance.

The eteplirsen application is still under review and it has not been determined that the benefits of the treatment outweigh the risks for the proposed indication. DMD is a progressive and lethal disease that has an early onset in childhood and is currently without any approved treatment. Furthermore, the likely prescribers of eteplirsen will be neurologists who specialize in the treatment of DMD and would have knowledge of both the disease and therapeutic options. Therefore, at this time, this reviewer is not recommending a REMS for the management of the identified risks.

5 CONCLUSION

In conclusion, if eteplirsen is approved, risk mitigation measures beyond the professional labeling are not warranted at this time to ensure the benefits outweigh the risks based on the identified risks, the likely prescribing community of specialists, and the lethal nature of the disease

Should DNP have any concerns or questions, or feel that a REMS may be warranted for this product, or if new safety information becomes available, please send a consult to DRISK.

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/s/

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05/03/2016

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