Title: Eteplirsen (Exondys 51) for Duchenne Muscular Dystrophy

**Description**

Duchenne muscular dystrophy is an inherited disorder that results in progressive muscle weakness and loss of muscle mass. It primarily affects boys. It occurs as a result of mutation(s) in the gene responsible for producing dystrophin, a cohesive protein that is
essential for maintaining muscle support and strength. Eteplirsen is an antisense oligonucleotide that induces skipping of exon 51 and thereby repairing the mutated reading frame. As a result, eteplirsen enables the production of an internally truncated, yet functional, dystrophin protein.

**Objective**

The objective of this evidence review is to assess the efficacy and safety of eteplirsen for treatment of individuals with confirmed mutation of the Duchenne muscular dystrophy gene that is amenable to exon 51 skipping.

**Background**

Duchenne muscular dystrophy (DMD) is an X-linked, recessive disorder that occurs in approximately 1 in every 3500 to 5000 boys. It primarily affects boys. However, a small number of girls are also affected, but remain asymptomatic and only rarely present with a mild form of the disease. According to U.S. epidemiologic data, the first signs or symptoms of DMD are noted at a mean age of 2.5 years (range, 0.2-1 years), and the mean age at definitive diagnosis is 4.9 years (range, 0.3-8.8 years). DMD occurs as a result of mutation(s) in the gene responsible for producing dystrophin, a cohesive protein that is essential for maintaining muscle support and strength. DMD is the longest known human gene and several mutations can cause DMD. Most deletion mutations disrupt the translational reading frame in the dystrophin mRNA resulting in an unstable, nonfunctional dystrophin molecule. As a result, there is progressive muscle degeneration leading to loss of independent ambulation, as well as other complications, including respiratory and cardiac complications. Genetic testing is required to determine the specific DMD gene mutation(s) for a definitive diagnosis, even when the absence of dystrophin protein expression has been confirmed by muscle biopsy. There are over 4700 mutations in the Leiden DMD mutation database and the most common mutations are concentrated between exons 45 and 53.

Eteplirsen is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) class. PMO are stable RNA analogues that selectively binds to exon 51 of the dystrophin premessenger RNA. This causes the exon to be skipped and prevents that part of the code from being read during mRNA processing, thereby repairing the mutated reading frame in the mRNA coding sequence in patients with a deletion in exons 45-50, 47-50, 48-50, 49-50, 50, 52, or 52-63 of this gene. As a result, eteplirsen enables the production of an internally truncated, yet functional, dystrophin protein.

The current standard of pharmacotherapy is corticosteroids for all patients regardless of genetic mutation. Treatment is initiated once patients reach a plateau of motor skill development, generally at ages 4 to 6 years, but prior to onset of motor decline. The goal of corticosteroid therapy is to preserve ambulation and minimize respiratory, cardiac, and orthopedic complications.
**Regulatory Status**
In September 2016, eteplirsen (Exondys 51™; Sarepta Therapeutics) was approved by the U.S. Food and Drug Administration through the orphan drug status process for use in Duchenne muscular dystrophy (DMD) patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. This indication was approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with eteplirsen.

**POLICY**
The use of eteplirsen is considered experimental / investigational for all indications, including, but not limited to the treatment of Duchenne muscular dystrophy

**Policy Guidelines**
The recommended dose of eteplirsen is 30 mg/kg of body weight administered once weekly as a 35- to 60-minute intravenous infusion. Eteplirsen is supplied in single-dose vials containing 100 mg or 500 mg (50 mg/mL).

**Rationale**
This evidence review was based on a search of the MEDLINE database. The most recent literature search was conducted through October 26, 2016.

**Study 201/202 (Pivotal Trial)**
In single-center, double-blind, placebo-controlled trial, 12 boys ages 7 to 13 years with Duchenne muscular dystrophy (DMD) amenable to exon 51 skipping and on stable corticosteroid dose for last 6 months were randomized to eteplirsen (30 or 50 mg/kg/wk) or placebo (4 patients per group). Treatment was continued to 24 weeks and then placebo patients switched to eteplirsen 30 or 50 mg/kg (n=2 per group) at week 25. All treatment subsequently became open-label and patients were followed for additional 24 weeks (48 weeks in total). The primary end point was dystrophin expression. Clinical end points such as 6-minute walk distance (6MWD) were also assessed. 6MWD measures the distance that a patient can walk on a flat, hard surface in a period of 6 minutes. Patients had a mean age of 9.4 years and a mean 6MWD at baseline of 363 meters.

**Dystrophin Levels**
The primary trial end point was a surrogate measure of change in dystrophin-positive fibers as measured in muscle biopsy tissue using immunohistochemistry. Serial biopsies were performed at 12, 24, and 48 weeks, although biopsies were performed on only half the treated patients at each of the 12- (only for eteplirsen 50-mg/kg group) and 24-week periods (only for eteplirsen 30-mg/kg group); all 12 patients were receiving drug treatment by week 48. The results published in 2013 reported substantial increase (range, 23%-52%) in the percentage of dystrophin-containing fibers in the biopsy specimens at week 24 and 48 in the eteplirsen-treated groups. However, immunohistochemistry analysis is not a quantitative measure of dystrophin. This analysis evaluates thin slices of muscle biopsies to assess if dystrophin is present or absent.
Each muscle fiber that shows any amount of dystrophin is counted as positive, regardless of the actual quantity of dystrophin present. On the other hand, Western blot analyzes how much dystrophin is present in a sample. Results reported in the prescribing label show the average dystrophin protein level after 180 weeks of treatment with eteplirsen measured by Western blot analysis of biopsy was 0.93% of the dystrophin level in healthy subjects. Further, a more rigorous and fully blinded reanalysis by 3 investigators of the immunohistochemical assay by the Food and Drug Administration (FDA) cast further doubt about the consistency of immunohistochemical analysis as there was little difference in positive fibers between original baseline samples and week 180.

6-Minute Walking Test
The prespecified clinical end points on 6MWT of study 201 (week 24) and study 202 (week 48) were negative. The published article reported a 67.3-meter benefit in 6MWT at week 48 in ambulation-evaluable eteplirsen-treated patients compared to placebo/delayed patients (p<0.005). However, this was a post hoc analysis as it excluded 2 eteplirsen-treated patients who deteriorated quickly while receiving therapy and lost ambulation at or beyond week 24. FDA has recommended retraction of the published study due to concerns related to interpretation of its findings. Further, in an exploratory analysis, FDA found no correlation between dystrophin levels and 6MWT. For example, among 4 patients with most preserved 6MWT, 2 had the lowest levels and 2 had the highest dystrophin levels as per Western blot. As per the prescribing label, there was no significant difference in change in 6MWD between patients treated with eteplirsen and placebo. While 6MWT may seemingly be an objective test, the results can also be influenced by expectation bias, motivation, and coaching especially in the context that patients in the pivotal 201/202 trial were aware of treatment assignment for majority of the investigation period.

Sarepta also claimed a gain of 162 meters in 6MWD at 4 years after treatment with eteplirsen in 12 patients in study 202 compared to data of 13 patients from an external control at the FDA peripheral and central nervous system drugs advisory committee. Results were subsequently published in a peer-reviewed journal. The data for external control was extracted from pooled data from an Italian and Belgium registry by matching corticosteroid use at baseline, availability of longitudinal data for 6MWT, age and genotype amenable to exon 51 skipping therapy. However, FDA and others have identified several issues related to the use of an external control such as differences in the use of steroids and physical therapy between the 2 groups. Most importantly, the impact of unknown prognostic factors cannot be ascertained in an externally controlled study.

FDA was unable to draw conclusions from the data of pivotal trials about whether eteplirsen increased dystrophin production as quantitative estimates of pretreatment dystrophin levels were not available. In June 2016, FDA requested Sarepta to submit additional data for review of eteplirsen. Sarepta complied with this request by submitting data of 13 patients from the ongoing PROMOVI trial for whom quantitative estimates of dystrophin at baseline and at week 48 were available. PROMOVI is a 96-week, open-label, multicenter, phase 3 study with a planned enrollment of 160 genotypically confirmed DMD patients; 80 patients amenable to exon 51 skipping will be treated with eteplirsen (30 mg/kg) and compared to 80 untreated group who are not amenable to exon 51 skipping. Male ambulatory patients aged between 7 to 16 years who are on stable dose of corticosteroids for at least 6 months and have intact right and left bicep muscles (the preferred biopsy site) or 2 alternative upper arm muscle groups will be included in the trial. The estimated completion date of this trial is January 2019. Subsequent FDA’s approval
was based on data of these 13 patients with a mean age of 8.9 years.\textsuperscript{4} In the 12 patients with evaluable results, the pretreatment dystrophin level was 0.16\%±0.12\% of the dystrophin level in a healthy subject and 0.44\%±0.43\% after 48 weeks of treatment with eteplirsen (p<0.05). Median increase after 48 weeks was 0.1\%. The clinical benefit of this increase in eteplirsen is unknown.

**Section Summary: Study 201/202 (Pivotal Trial)**
The clinical benefit of treatment for DMD with eteplirsen, including improved motor function, has not been demonstrated. Establishment of a clinical benefit is warranted in ongoing clinical trials.

**Harms**
The most frequently reported adverse events across clinical trials were balance disorder, vomiting, and contact dermatitis.\textsuperscript{4}

**Summary of Evidence**
For individuals with confirmed mutation of the Duchenne muscular dystrophy gene that is amenable to exon 51 skipping who are treated with eteplirsen, the evidence includes 1 randomized controlled trial (RCT) and its open-labelled follow-up study, and interim data from an ongoing RCT. Relevant outcomes are disease-specific survival, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. As per Food and Drug Administration analysis, the pivotal RCT and its open-labelled follow-up study failed to provide evidence of a clinical benefit in terms of 6-minute walk distance. Evidence regarding impact of eteplirsen treatment on dystrophin levels was inconclusive. Interim results from an ongoing study provided evidence that eteplirsen increased dystrophin levels in skeletal muscle in some patients by a median of 0.1\% after 48 weeks of treatment. In summary, the clinical benefit of treatment for Duchenne muscular dystrophy with eteplirsen, including improved motor function, has not been demonstrated. Establishment of a clinical benefit is warranted in ongoing clinical trials. The most frequently reported adverse events across clinical trials were balance disorder, vomiting and contact dermatitis. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Practice Guidelines and Position Statements**
The U.S. Centers for Disease Control and Prevention has developed care recommendations.\textsuperscript{1,14} These recommendations focus on the overall perspective on care, pharmacological treatment, psychosocial management, rehabilitation, orthopedic, respiratory, cardiovascular, gastroenterology/nutrition, and pain issues, in addition to general surgical and emergency room precautions. They recommend the use of corticosteroids to slow the decline in muscle strength and function in Duchenne muscular dystrophy (DMD). The working group does not make recommendations on the use of any other drugs or dietary supplements and does not mention eteplirsen in the recommendations.

**U.S. Preventive Services Task Force Recommendations**
Not applicable.

**Ongoing and Unpublished Clinical Trials**
A search of ClinicalTrials.gov in September 2016 did not identify any ongoing or unpublished trials that would likely influence this review.
The Food and Drug Administration, under the accelerated approval regulations, 21 CFR 314.510, requires that Sarepta 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/wk) or to a dosage that provides significantly higher exposure (eg, 30 mg/kg daily). The primary end point will be the North Star Ambulatory Assessment.\textsuperscript{15}

**CODING**

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

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<td>J3490</td>
<td>Unclassified drugs [when specified as eteplirsen]</td>
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<tr>
<td>J3590</td>
<td>Unclassified biologics [when specified as eteplirsen]</td>
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**DIAGNOSES**

Experimental / Investigational for all diagnoses related to this medical policy.

**REVIZIONS**

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**REFERENCES**


