Eteplirsen (Exondys 51) for Duchenne Muscular Dystrophy

**Title:** Eteplirsen (Exondys 51) for Duchenne Muscular Dystrophy

**Professional**
- Original Effective Date: January 19, 2017
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<table>
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<tr>
<th>Populations</th>
<th>Interventions</th>
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<th>Outcomes</th>
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<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
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- With a confirmed variant of the Duchenne muscular dystrophy gene that is amenable to exon 51 skipping | • Eteplirsen | • Continued medical management (eg, glucocorticoids) | • Disease-specific survival |

**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
variant(s) in the gene responsible for producing dystrophin, a cohesive protein 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 variant of the Duchenne muscular dystrophy gene that is amenable to exon 51 skipping.

**Background**

**DUCHENNENE MUSCULAR DYSTROPHY**
Duchenne muscular dystrophy (DMD) is an X-linked, recessive disorder that occurs in approximately 1 in every 3500 to 5000 boys.\(^1\) It primarily affects boys. However, a small number of girls are also affected, but they are usually asymptomatic and even when symptomatic, only 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).\(^2\) DMD occurs as a result of variant(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 variants disrupt the translational reading frame in the dystrophin mRNA (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.\(^3\) Genetic testing is required to determine the specific DMD gene variants(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 variants are concentrated between exons 45 and 53.

**Treatment**
Eteplirsen is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer class. Phosphorodiamidate morpholino oligomer oligomer are stable oligonucleotide analogues that selectively bind to RNA to alter gene expression. In the case of eteplirsen, the phosphorodiamidate morpholino oligomer binds to exon 51 of the dystrophin pre-mRNA causing the exon to be skipped and prevents that part of the code from being read during mRNA processing, thereby partially repairing the mutated reading frame in the mRNA coding sequence. As a result, eteplirsen enables the production of an internally truncated, yet functional, dystrophin protein.

The current standard of pharmacotherapy for DMD is corticosteroids for all patients regardless of genetic variant. Treatment is initiated once patients reach a plateau of
motor skill development, generally at ages 4 to 6 years, but before the onset of motor decline. The goal of corticosteroid therapy is to preserve ambulation and minimize respiratory, cardiac, and orthopedic complications.¹

**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 variant 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 has been updated with searches of the MEDLINE database. The most recent literature update was performed through November 1, 2017.

**ETEPLIRSEN FOR TREATMENT OF DUCHENNE MUSCULAR DYSTROPHY (DMD)**

**Studies 201 and 202 (Pivotal Trial)**

In a single-center, double-blind, placebo-controlled trial, 12 boys ages 7 to 13 years with 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 continued for 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 an additional 24 weeks (48 weeks in total). The primary endpoint was dystrophin expression. Clinical endpoints such as distance on the 6-minute walk test (6MWT) were also assessed. The 6MWT measures the distance that a patient can walk on a flat, hard surface in 6 minutes. Mean age was 9.4 years and mean 6MWT distance at baseline was 363 meters.⁴,⁵

**Dystrophin Levels**

The primary trial endpoint was a surrogate measure of change in dystrophin-positive fibers as measured in muscle biopsy tissue using immunohistochemistry.⁶ Serial biopsies were performed at 12, 24, and 48 weeks, although biopsies were performed on only half of the treated patients at each of the 12- (only for the eteplirsen 50-mg/kg group) and 24- (only for the eteplirsen 30-
mg/kg group) week periods; all 12 patients were receiving drug treatment by week 48. The results published in 2013 reported a substantial increase (range, 23%-52%) in the percentage of dystrophin-containing fibers in the biopsy specimens at weeks 24 and 48 in the eteplirsen-treated groups.\(^5\) However, immunohistochemistry analysis is not a quantitative measure of dystrophin. This analysis evaluates thin slices of muscle biopsies to assess whether dystrophin is present or absent. Each muscle fiber showing any amount of dystrophin counts 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 showed 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.\(^4\) 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 because there was little difference in positive fibers between original baseline samples and week 180.\(^7\)

**6-Minute Walking Test**
The prespecified clinical endpoints on the 6MWT for study 201 (week 24) and study 202 (week 48) were negative.\(^7\) The published article reported a 67.3-meter benefit in 6MWD at week 48 in ambulation-evaluable eteplirsen-treated patients compared with placebo/delayed patients (\(p<0.005\)).\(^5\) However, this was a post hoc analysis because it excluded 2 eteplirsen-treated patients who quickly deteriorated while receiving therapy and lost ambulation at or beyond week 24. FDA has recommended retraction of the published study due to concerns about the interpretation of its findings.\(^8\) Further, in an exploratory analysis, FDA found no correlation between dystrophin levels and 6MWD.\(^7\) For example, among four patients with the most preserved 6MWT, distance two had the lowest, and two had the highest dystrophin levels using per Western blot. As per the prescribing label, there was no significant difference in change in 6MWT distance between patients treated with eteplirsen and placebo. While the 6MWT may be an objective instrument, its results can 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 most the investigation period.

Eteplirsen's manufacturer reported a gain of 162 meters on the 6MWT at 4 years after treatment with eteplirsen in 12 patients in study 202 compared with 13 patients from an external control at the FDA Peripheral and Central Nervous System Drugs Advisory Committee meeting.\(^6\) Results were subsequently published in 2016 in a peer-reviewed journal.\(^9\) Data for external control were extracted from pooled data from an Italian and Belgian registry by matching corticosteroid use at baseline, availability of longitudinal data for the 6MWT, age, and genotype amenable to exon 51 skipping therapy. However, FDA\(^10\) and others\(^11\) 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 two groups. Most importantly, the impact of unknown prognostic factors cannot be ascertained in an externally controlled study.

FDA was unable to conclude from the pivotal trial data about whether eteplirsen increased dystrophin production because quantitative estimates of pretreatment dystrophin levels were not available. In June 2016, FDA requested that Sarepta submit additional eteplirsen data for review.\(^12\) Sarepta complied with this request, submitting data of 13 patients from the ongoing PROMOVI trial for whom quantitative estimates of dystrophin at baseline and week 48 were available. PROMOVI is a 96-week, open-label, multicenter, phase 3 study with a planned...
enrollment of 160 patients with genotype-confirmed DMD; 80 patients amenable to exon 51 skipping will be treated with eteplirsen (30 mg/kg) and compared with 80 untreated patients not amenable to exon 51 skipping. Male ambulatory patients between 7 and 16 years of age who are on stable doses of corticosteroids for at least 6 months and have intact right and left bicep muscles (the preferred biopsy site) or 2 other 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 for these 13 patients (mean age, 8.9 years). In the 12 patients with evaluable results, the mean (standard deviation) 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 eteplirsen treatment (p<0.05). Median increase after 48 weeks was 0.1%. The clinical benefit of this dystrophin increase is unknown.

Section Summary: Studies 201 and 202
The clinical benefit of treating DMD with eteplirsen, including improved motor function, has not been demonstrated. Establishing a clinical benefit is necessary for ongoing clinical trials.

Harms
The most frequently reported adverse events across the clinical trials were balance disorder, vomiting, and contact dermatitis. 4

SUMMARY OF EVIDENCE
For individuals with a confirmed variant of the Duchenne muscular dystrophy gene that is amenable to exon 51 skipping who receive eteplirsen, the evidence includes a randomized controlled trial and its open-labeled follow-up study, and interim data from an ongoing randomized control trial. 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. According to the Food and Drug Administration analysis, the pivotal randomized control trial and its open-labeled follow-up failed to provide evidence of a clinical benefit regarding 6-minute walk distance. Evidence on the 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. Establishing a clinical benefit is necessary for 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
Centers for Disease Control and Prevention
The U.S. Centers for Disease Control and Prevention has developed care recommendations. They focus on the overall perspective on care, pharmacologic treatment, psychosocial management, rehabilitation, orthopedic, respiratory, cardiovascular, gastroenterology and nutrition, and pain issues, as well as general surgical and emergency room precautions. The U.S. Centers for Disease Control and Prevention recommended the use of corticosteroids to slow the decline in muscle strength and function in Duchenne muscular dystrophy. The U.S. Centers for
Disease Control and Prevention did not make recommendations on the use of any other drugs or dietary supplements and did not mention eteplirsen in the recommendations.

**American Heart Association**
A 2017 statement from the American Heart Association addressed the treatment of cardiac issues in individuals with any of several neuromuscular diseases, including Duchenne muscular dystrophy. For patients with Duchenne muscular dystrophy, the Association recommended the use of glucocorticoids, among other medications. The statement does not address the use of eteplirsen. One of the statement’s coauthors disclosed being as an industry-supported investigator for the drug.

**U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS**
Not applicable.

**ONGOING AND UNPUBLISHED CLINICAL TRIALS**
A search of ClinicalTrials.gov in November 2017 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 with a confirmed variant 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/d). The primary endpoint will be the North Star Ambulatory Assessment.

**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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<th>HCPCS</th>
<th>Description</th>
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<td>J1428</td>
<td>Injection, eteplersen, 10mg</td>
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**DIAGNOSES**
Experimental / Investigational for all diagnoses related to this medical policy.

**REVISIONS**
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REFERENCES


