

Medical Policy



Title: Eteplirsen (Exondys 51) for Duchenne Muscular Dystrophy

Professional

Original Effective Date: January 19, 2017
 Revision Date(s): January 19, 2017;
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Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> With a confirmed variant of the Duchenne muscular dystrophy gene that is amenable to exon 51 skipping 	Interventions of interest are: <ul style="list-style-type: none"> Eteplirsen 	Comparators of interest are: <ul style="list-style-type: none"> Continued medical management (eg, glucocorticoids) 	Relevant outcomes include: <ul style="list-style-type: none"> Disease-specific survival Change in disease status Morbid events Functional outcomes Health status measures Quality of life Treatment-related mortality Treatment-related morbidity

DESCRIPTION

Duchenne muscular dystrophy (DMD) is an inherited disorder that results in progressive muscle weakness and loss of muscle mass, primarily affecting males. DMD is caused by variant(s) in the exon 51 gene responsible for producing dystrophin, a cohesive protein essential for maintaining muscle support and strength. The variant(s) disrupt the

translational reading of messenger RNA resulting in an unstable, nonfunctional dystrophin molecule. 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 determine whether eteplirsen improves the net health outcome of individuals with a confirmed variant of the Duchenne muscular dystrophy gene that is amenable to exon 51 skipping compared with medical management.

Background

DUCHENNE 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 males. 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 Symptoms include motor difficulties such as running, jumping, walking up stairs, and an unusual waddling gait. Some improvement in symptoms may be seen from three to six years of age, though gradual deterioration resumes and most patients lose ambulation by age 12 and require noninvasive ventilation (NIV) by late teenage years. Patients progress from needing NIV only during night sleeping, followed by NIV during day and night sleeping, and then NIV during day and night over the course of five to ten years.

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 messenger RNA (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

Patients with DMD should receive multidisciplinary care. In addition to muscle weakness and pain, cardiac, pulmonary, orthopedic, and endocrine symptoms should be managed. The current standard of pharmacotherapy for DMD is corticosteroids for all patients

regardless of the genetic variant. Treatment is initiated once patients reach a plateau of motor skill development, generally at ages four to six 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

Eteplirsen is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer class. Phosphorodiamidate morpholino 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.

Drisapersen was another exon 51 skipping treatment in development for the treatment of DMD. In 2016, when the phase 3 trial for drisapersen did not meet prespecified endpoints, the manufacturer discontinued development of this drug. The Food and Drug Administration had issued a complete response letter to the application concluding that the standard of substantial evidence of effectiveness had not been met.

Regulatory Status

In September 2016, eteplirsen (Exondys 51™; Sarepta Therapeutics) was approved by the U.S. Food and Drug Administration after orphan drug designation for 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.

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.⁴

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 October 1, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

eteplirsen for treatment of Duchenne muscular dystrophy

Clinical Context and Therapy Purpose

The purpose of eteplirsen in patients who have a confirmed variant of the *DMD* gene that is amenable to exon 51 skipping, is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of eteplirsen in patients with the *DMD* gene variant that is amenable to exon 51 skipping improve the net health outcome compared with medical management with glucocorticoids?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are patients with a confirmed variant of the *DMD* gene that is amenable to exon 51 skipping.

Interventions

The therapy being considered is eteplirsen, which is a stable oligonucleotide analogue that selectively binds to RNA to alter gene expression. Eteplirsen binds to exon 51, causing the exon to be skipped. Skipping exon 51 enables the production of functional dystrophin in muscle.

Recommended dosage is 30 mg/kg body weight once weekly, administered as an intravenous infusion over 35 to 60 minutes.

Comparators

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

Outcomes

The general outcomes of interest are dystrophin level, functional outcomes such as the 6-minute walk test (6MWT), lung function (forced vital capacity), and the North Star Ambulatory Assessment (NSAA). Additional outcomes of interest include adverse events.

Measuring dystrophin level in muscle fibers has been a proposed outcome, though the correlation between dystrophin levels and clinically meaningful outcomes is unclear. Measuring dystrophin levels may be conducted by:

- An immunohistochemical analysis of muscle biopsy tissue. Thin slices of biopsy tissue are evaluated to detect the presence or absence of dystrophin. Each muscle fiber showing any amount of dystrophin counts as positive, regardless of the actual quantity of dystrophin present. The amount of dystrophin is not calculated with this method.
- Western blot analysis. In this method, muscle tissue samples undergo a protein denaturation, followed by gel electrophoresis which can quantify the amount of dystrophin in the muscle tissues.

The 6MWT measures the distance that a patient can walk on a flat, hard surface in a period of 6 minutes. The 6MWT can offer information on the global and interrelated components of exercise such as extremity strength, biomechanical inefficiencies, endurance, and cardiorespiratory status. It has also been used as a measure of the quality of life. Determining the minimum clinically important difference in 6MWT is challenging in patients with DMD, as the rate of progression of the disease varies among patients. Estimates of minimum clinically important difference for DMD patients of a change of 30 meters have been reported.^{5,6} Interpretation of 6MWT results is limited by the variability in testing procedures and patient motivation.

Forced vital capacity (FVC), measured by spirometry, is the amount of air forcibly exhaled after taking the deepest breath possible. FVC is used to monitor lung function in DMD patients. Steroid therapy has the potential to stabilize or delay the loss of lung function in DMD patients.

The NSAA, developed by the North Star Clinical Network and supported by the Muscular Dystrophy Campaign, is a method to monitor the progression of DMD and treatment effects. Seventeen activities are graded as "normal" (2 points); "modified" (1 point); or "unable to achieve independently" (0 points). For each activity, the NSAA has clear instructions to the health care provider on coaching the patient on starting positions and test details. The activities include: standing still; walking; standing from a chair; standing on the right leg; standing on the left leg; climbing onto a box 15 cm in height using right leg first; climbing onto the box using left leg first; descending the box using right leg first; descending the box using the left leg first; sitting up from lying position; rising from the floor; lifting head to look at toes; standing on heels; jumping; hopping on right leg; hopping on left leg; and running 10 meters.

Adverse events include balance disorder and vomiting.

Timing

Follow-up measurements can be taken within weeks of initial treatment. As DMD is a progressive disease, follow-up continues during the entire course of treatment.

Setting

Eteplirsen is administered intravenously, which can be performed in infusion centers or in tertiary care facilities. Monitoring of treatment may be conducted by neurologists, orthopedists, physiatrists, and/or primary care physicians.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trial and Open-Label Extension Study Studies 201 and 202 (Pivotal Trial)

In a single-center, double-blind, placebo-controlled trial (Study 201), 12 males ages 7 to 13 years with DMD amenable to exon 51 skipping and on stable corticosteroid dose for at least 6 months were randomized to eteplirsen (30 or 50 mg/kg/wk) or placebo (4 patients per group) (see Table 1). Treatment continued for 24 weeks and then placebo patients switched to eteplirsen 30 or 50 mg/kg (n=2 per group) at week 25 (Study 202). All treatment subsequently became open-label and patients were followed for an additional 24 weeks (48 weeks in total) (see Table 1).^{7,8}

Dystrophin Levels

The primary trial endpoint was a measure of change in dystrophin-positive fibers as measured in muscle biopsy tissue using immunohistochemistry.⁹ 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 (see Table 2).⁸ 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.⁷ 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 180.¹⁰

6-Minute Walking Test

The prespecified clinical endpoints on the 6MWT for study 201 (week 24) and study 202 (week 48) were negative (see Table 2).¹⁰ The article reported a 67.3-meter benefit in 6MWD at week 48 in ambulation-evaluable eteplirsen-treated patients (n=6) compared with placebo/delayed patients (p<0.005).⁸ However, this was a post hoc analysis excluding two eteplirsen-treated patients who quickly deteriorated while receiving therapy and lost ambulation beginning at week four of the trial. The FDA has recommended retraction of the published study due to concerns about the interpretation of its findings.¹¹ Further, in an exploratory analysis, the FDA found no correlation between dystrophin levels and 6MWD.¹⁰ For example, among the four patients with the most preserved 6MWT, two had the lowest and two had the highest dystrophin levels determined by 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.⁹ Results were subsequently published by Medell et al (2016) in a peer-reviewed journal.¹² Data for external controls 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, the FDA¹³, and others¹⁴ 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.

The 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, the FDA requested that Sarepta et al (2016) submit additional eteplirsen data for review.¹⁵ Sarepta et al (2016) complied with this request, submitting preliminary data of 12 patients from the ongoing PROMOVI trial in which 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 (see Table 1).¹⁶ The estimated completion date of this trial is February 2020. The FDA's approval was based on data for these 12 patients (mean age, 8.9 years).⁷ Levels of dystrophin were significantly higher after 48 weeks of treatment compared with baseline (see Table 2). The clinical benefit of this dystrophin increase is unknown.

Harms

The most frequently reported adverse events in the first 24 weeks of the study among the 8 patients treated with eteplirsen were balance disorder (n=3), vomiting (n=3), and contact dermatitis (n=2).⁷

Common treatment-emergent adverse events reported among the 12 patients during the 12-week RCT include: procedural pain (n=7), oropharyngeal pain (n=6), hypokalemia (n=6), gastrointestinal disorders (n=5), cough (n=4), and extremity pain (n=4).⁸

Table 1. Summary of Key Study Characteristics

Study; Trial	Country	Design	Sites	Duration	Participants	Interventions	
						Active	Comparator
Mendell et al (2013) ⁸ ; Study 201	U.S.	RCT	1	24 wk	Patients with DMD ages 7-13 y with confirmed deletions amenable to skipping exon 51 and ability to walk 200-400 m on 6MWT and on glucocorticoids for ≥24 wk	eteplirsen 30 mg/kg/wk (n=4); eteplirsen 50 mg/kg/wk (n=4)	Placebo (n=4)
Mendell et al (2013) ⁸ ; Study 202	U.S.	Open-label	1	24 wk	Patients from RCT described above, in which patients in the active arms continued with treatment and patients in placebo arm were rolled over to open-label delayed eteplirsen	eteplirsen 30 mg/kg/wk (n=4); eteplirsen 50 mg/kg/wk (n=4); delayed eteplirsen 30 mg/kg/wk (n=2); delayed eteplirsen 50 mg/kg/wk (n=2)	
Sarepta et al (2016) ^{7,16,a}	U.S.	Open-label, ongoing study	37	96 wk	Patients with DMD ages 7-16 y with confirmed deletions amenable to skipping exon 51 and ability to walk >300 m on 6MWT and on glucocorticoids for ≥24 wk	eteplirsen 30 mg/kg/wk (n=12); target is 80 patients	There will be untreated controls of patients with DMD not amenable to exon 51 skipping

DMD: Duchenne muscular dystrophy; RCT: randomized controlled trial; 6MWT: 6-minute walk test.

^a This study is ongoing (PROMOVI; NCT02255552). The Food and Drug Administration asked Sarepta for additional data for review and Sarepta provided information on 13 patients currently enrolled in the PROMOVI trial who had baseline and 48-week data.

Table 2. Summary of Key Study Results

Study	Mean Percent Change in Dystrophin Level From Baseline (SE)			Mean Change in 6MWT (SE), Meters	
	Study 201		Study 202	Study 201	Study 202
	Week 12	Week 24	Week 48	Week 24	Week 48
Mendell et al (2013) ⁸					
All eteplirsen (n=8)	NR	NR	47.3 (3.9) ^a	NR	NR
30-mg (n=4)	NR	22.9 (2.9) ^a	51.7 (3.5) ^a	14.2 (14.4) ^b	31.5 (19.9) ^{b, c}
50-mg (n=4)	0.8 (3.5)	NR	42.9 (6.7) ^a	-0.3 (31.2)	21.0 (38.2) ^c
Placebo (n=4)	-4.0 (2.9)	-4.0 (2.9)	37.7 (6.3) ^a	-25.8 (30.6)	-68.4 (37.6)
30-mg delayed (n=2)	NR	-7.5 (1.0)	33.6 (5.2)	NR	NR
50-mg delayed (n=2)	-0.6 (5.2)	NR	41.8 (13.3)	NR	NR

Study	Mean Percent Change in Dystrophin Level From Baseline (SE)			Mean Change in 6MWT (SE), Meters	
	Mean Percent Normal Dystrophin (SD)				
	Baseline	Week 48	p		
Sarepta et al (2016) ^{7,16,}	0.16 (0.12)	0.44 (0.43)	0.008		

NR: not reported; SD: standard deviation; SE: standard error; 6MWT: 6-minute walk test.

^a p<0.01 vs baseline

^b Excluding 2 patients who showed rapid disease progression at week 4 of study.

^c p<0.001 vs delayed eteplirsen group.

The purpose of gaps tables (see Tables 3 and 4) is to display notable gaps identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 3. Relevance Gaps

Study; Trial	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
Mendell et al (2013) ⁸ ; Study 201				2. Primary end point was physiologic measure (dystrophin level) and correlation with clinical benefit is unknown 4. Dystrophin measured by IHC staining which only reports presence or absence, vs Western blot which measures quantity of dystrophin	
Mendell et al (2013) ⁸ ; Study 202				2. Primary end point was physiologic measure (dystrophin level) and correlation with clinical benefit is unknown 4. Dystrophin measured by IHC staining which only reports presence or absence, vs Western blot which measures quantity of dystrophin	
Sarepta et al (2016) ^{7,16,}				2. Primary end point was physiologic measure (dystrophin level) and correlation with clinical benefit is unknown	

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

IHC: immunohistochemical.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 4. Study Design and Conduct Gaps

Study	Allocation ^a	Blinding ^b	Selective Reporting ^d	Data Completeness ^e	Power ^d	Statistical ^f
Mendell et al (2013) ⁸ ; Study 201	3. No description of randomization procedure or subsequent concealment			5. Two of 8 patients in treatment arms who lost ambulation were excluded from 6MWT analysis	1. Small sample size (each arm had 4 patients)	
Mendell et al (2013) ⁸ ; Study 202		1.-3. Open-label extension study			1. Small sample size (arms had 2 or 4 patients)	
Sarepta et al (2016) ^{7,16}		1.-3. Open-label study		1. Preliminary results of an ongoing study (results from 12 of an expected 80 population) and no comparator data provided at this point	1. Preliminary results on 12 patients	

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Gaps tables bullet points:

- Small sample size
- Primary outcome was a physiologic measurement without a known correlation with clinical benefit. In addition, the physiologic outcome was not measured using the most accurate technique available in two of the three studies.

Observational Study

Kinane et al (2018) conducted a case-control study of long-term pulmonary function in patients with DMD treated with eteplirsen compared with historical controls.¹⁷ Cases were patients from the RCT by Mendell et al (2013) described above (n=12) and historical controls were patients between 7 years and 15.5 years in the United Dystrophinopathy Project who had undergone pulmonary function testing (n=34). All patients in the United Dystrophinopathy Project had confirmed dystrophin variant. The annual decline in FVC was not significantly different between groups. The annual decrease in FVC in the historical controls was 4.1% (95% confidence interval, 1.9% to 6.3%) and the annual decrease in FVC in the cases treated with eteplirsen was 2.3% (95% confidence interval, 1.2% to 3.4%).

Systematic Reviews

Randeree et al (2018) conducted a pooled analysis of studies evaluating the use of eteplirsen for the treatment of patients with DMD.¹⁸ A literature search, conducted through November 2017, identified 3 studies (N=38 patients) for inclusion in the analyses. The 3 studies consisted of a nonrandomized dose-escalation study (n=7), an open-label dose-escalation study (n=19), and the Mendell et al (2013) study described above (n=12). A quality assessment of the studies was not performed. The average increase in percent dystrophin-positive fibers was 24.2% (standard deviation, 24.4%) and the average rate of decline in 6MWT was 65 m (standard deviation=100.1). The clinical significance of these results is unclear.

Section Summary: Eteplirsen for Treatment of DMD

Evidence for the use of eteplirsen for the treatment of DMD amenable to exon 51 skipping includes an RCT, an open-label extension of the RCT, a case-control study using historical controls, and preliminary results from a larger open-label study. The single RCT had a sample of 12 patients and the larger open-label study providing preliminary results also had 12 patients. No power calculations were made to determine if these sample sizes were adequate to detect treatment effect.

Additional limitations involve the primary physiologic outcome of dystrophin level, both in how the level was measured and in how the level correlates with a meaningful clinical outcome. While treatment with eteplirsen may increase dystrophin levels detected in muscle fibers, the impact of these levels on clinical measurements is unclear.

The outcome of 6MWT showed significant differences between patients receiving eteplirsen at the beginning of the RCT compared with patients receiving delayed eteplirsen. However, interpreting the 6MWT results has limitations due to differences in how the test is conducted and how motivated the patients are. A more objective measure of pulmonary function, FVC, was evaluated in a case-control study using data from patients in the RCT compared with historical controls. This analysis reported a lower decrease in FVC in patients receiving eteplirsen; however, the difference was not statistically significant, possibly due to insufficient power.

The clinical benefit of treating DMD with eteplirsen, including improved motor function and pulmonary function, has not been demonstrated. Establishing a clinical benefit is necessary for ongoing clinical trials.

Summary of Evidence

For individuals with a confirmed variant of the DMD gene that is amenable to exon 51 skipping who receive eteplirsen, the evidence includes a randomized controlled trial (RCT) and its open-labeled follow-up study, a case-control study using historical controls, and interim data from an ongoing larger open-label comparative study. The 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. The single RCT had a sample of 12 patients and the larger open-label study providing interim results also had 12 patients. No power calculations were made to determine if these sample sizes were adequate to detect treatment effect. The primary physiologic outcome of dystrophin level in these studies is questionable, both in how the level was measured and in how the level correlates with a meaningful clinical outcome. While treatment with eteplirsen may increase dystrophin levels detected in muscle fibers, the impact of these levels on clinically meaningful outcomes is unclear. The outcome of

the 6-minute walk test showed significant differences between patients receiving eteplirsen at the beginning of the RCT compared with patients receiving delayed eteplirsen. However, interpreting the 6-minute walk test results has limitations due to differences in how the test may be conducted and patient motivation. A more objective measure of pulmonary function (forced vital capacity) was evaluated in a case-control study using data from patients in the RCT compared with historical controls. This analysis reported a lower decrease in forced vital capacity in patients receiving eteplirsen; however, the difference was not statistically significant, possibly due to insufficient power. In summary, the clinical benefit of treatment for DMD 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 convened a DMD Care Considerations Working Group. The Group developed care recommendations in 2010 and updated them in 2018.^{1,19,20,21,22} They recommendations 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 Centers for Disease Control and Prevention recommended the use of corticosteroids to slow the decline in muscle strength and function in Duchenne muscular dystrophy (DMD). The Working Group did not make recommendations on the use of eteplirsen. However, eteplirsen is discussed briefly under the section on "Emerging treatments."²² The Working Group stated that eteplirsen was approved by the Food and Drug Administration in 2016 for males with the dystrophin gene variant amenable to exon 51 skipping, which is about 13% of the males with DMD.

American Heart Association

A statement from the American Heart Association (2017) addressed the treatment of cardiac issues in individuals with any of several neuromuscular diseases, including DMD.²³ For patients with DMD, 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 an industry-supported investigator for the drug.

American Academy of Neurology

The American Academy of Neurology (2016) published an updated practice guideline on the use of corticosteroids for the treatment of DMD.²⁴ The Academy does not discuss the use of eteplirsen for DMD.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 5.

Table 5. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01540409 ^a	Open-Label, Multiple-Dose, Efficacy, Safety, and Tolerability Study of Eteplirsen in Subjects with Duchenne Multiple Dystrophy Who Participated in Study 4658-US-201	12	Feb 2017 (ongoing)
NCT02420379 ^a	An Open-Label, Multi-Center Study to Evaluate the Safety, Efficacy, and Tolerability of Eteplirsen in Early Stage Duchenne Muscular Dystrophy	40	Jan 2019
NCT02255552 ^a	An Open-Label, Multi-Center Study with a Concurrent Untreated Control Arm to Evaluate the Efficacy and Safety of Eteplirsen in Duchenne Muscular Dystrophy	110	Feb 2020
NCT03218995 ^a	An Open-Label Safety, Tolerability, and Pharmacokinetics Study of Eteplirsen in Young Patients with Duchenne Muscular Dystrophy Amenable to Exon 51 Skipping	12	Aug 2020

^a Denotes industry sponsorship or co-sponsorship.

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.

HCPCS

- 96365 Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
- J1428 Injection, eteplirsen, 10mg

DIAGNOSES

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

REVISIONS

01-19-2017	Policy added to bcbsks.com web site 12-20-2016. Policy effective 01-19-2017.
12-29-2017	Description section updated
	Rationale section updated
	In Coding section: <ul style="list-style-type: none"> ▪ Removed HCPCS Codes: J3490, J3590 ▪ Added HCPCS Code: J1428 (Effective 01-01-2018)
	References updated
03-13-2019	Description section updated
	Rationale section updated
	References updated

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