Policy Number	**RX501.084**
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Eteplirsen

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For Illinois only: Illinois Public Act 103-0458 [Insurance Code 215 ILCS 5/356z.61] (HB3809 Impaired Children) states all group or individual fully insured PPO, HMO, POS plans amended, delivered, issued, or renewed on or after January 1, 2025 shall provide coverage for therapy, diagnostic testing, and equipment necessary to increase quality of life for children who have been clinically or genetically diagnosed with any disease, syndrome, or disorder that includes low tone neuromuscular impairment, neurological impairment, or cognitive impairment.

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as

safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Eteplirsen (Exondys 51™) for the treatment of Duchenne muscular dystrophy **is considered not medically necessary** as a clinical benefit has not been established.

Eteplirsen (Exondys 51™) for the treatment of all other indications **is considered experimental, investigational and/or unproven.**

Policy Guidelines

None.

Description

Duchenne muscular dystrophy is an inherited disorder that results in progressive muscle weakness and loss of muscle mass, primarily affecting males. Duchenne muscular dystrophy results from non-sense or frame-shifting variant(s) in the *Duchenne muscular dystrophy* gene, which is responsible for producing dystrophin, a cohesive protein essential for maintaining muscle support and strength. Antisense oligonucleotides are short, synthetic, single-stranded oligodeoxynucleotides that selectively bind to specific exons of the dystrophin pre-messenger RNA causing the exon to be skipped and thereby repairing the mutated reading frame resulting in production of an internally truncated, yet functional, dystrophin protein. Eteplirsen has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of Duchenne muscular dystrophy which targets skipping of exon 51.

Background

Duchenne Muscular Dystrophy

Duchenne muscular dystrophy is an X-linked, recessive disorder that occurs in approximately 1 in every 3500 to 5000 males. (1) It primarily affects males. However, a small number of females are also affected, but are usually asymptomatic. Even when symptomatic, most females typically only present with a mild form of the disease. According to U.S. epidemiologic data, the first signs or symptoms of Duchenne muscular dystrophy 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, and walking upstairs, along with an unusual waddling gait. Some improvement in symptoms may be seen from 3 to 6 years of age, though gradual deterioration resumes, and most patients lose ambulation by age 12 and require noninvasive ventilation by the late teenage years. Patients progress from needing noninvasive ventilation only during night sleeping, followed by noninvasive ventilation during day and night sleeping, and then noninvasive ventilation during day and night over the course of 5 to 10 years.

Duchenne muscular dystrophy 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. *Duchenne muscular dystrophy* is the longest known human gene, and several variants can cause Duchenne muscular dystrophy. Most deletion variants disrupt the translational reading frame in the dystrophin messenger RNA 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 *Duchenne muscular dystrophy* gene variant(s) for a definitive diagnosis, even when the absence of dystrophin protein expression has been confirmed by muscle biopsy. There are over 4700 variants in the Leiden Duchenne muscular dystrophy mutation database, and the most common variants are concentrated between exons 45 and 53.

Regulatory Status

In September 2016, eteplirsen (Exondys 51™; Sarepta Therapeutics) was approved by the U.S. FDA for treatment of Duchenne muscular dystrophy patients who have a confirmed variant of the *Duchenne muscular dystrophy* 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. (4)

The FDA, under the accelerated approval regulations (21 CFR 314.510), requires that Sarepta conduct a confirmatory trial to demonstrate the clinical benefit of eteplirsen. In the 3 years after the FDA approval, there has still been no publication of a trial confirming or refuting a clinical benefit of eteplirsen. The European Medicines Agency rejected marketing approval for eteplirsen in September 2018. (5)

Rationale

This medical policy was created in June 2017 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through February 13, 2023.

Medical policies 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 (QOL) 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, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 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.

Antisense Oliogonucleotides for Treatment of Duchenne Muscular Dystrophy

Clinical Context and Therapy Purpose

The purpose of antisense nucleotides such as eteplirsen in patients who have a confirmed variant of the *Duchenne muscular dystrophy* gene that is amenable to specific 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 medical policy is: Does the use of eteplirsen in patients with a *Duchenne muscular dystrophy* gene variant that is amenable to exon skipping, improve the net health outcome compared with continued medical management?

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is patients with a confirmed variant of the *Duchenne muscular dystrophy* gene that is amenable to specific exon skipping.

Interventions

The therapies being considered are antisense oligonucleotides such as eteplirsen. 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-messenger RNA causing the exon to be skipped and prevents that part of the code from being read during messenger RNA processing, thereby partially repairing the mutated reading frame in the messenger RNA coding sequence. As a result, eteplirsen enables the production of an internally truncated, yet functional, dystrophin protein.

Comparators
The following practice is currently being used to treat patients with a confirmed variant of the *Duchenne muscular dystrophy* gene: standard multidisciplinary care including pharmacotherapy. Pharmacotherapy primarily involves 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 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. In addition, muscle weakness and pain, cardiac, pulmonary, orthopedic, and endocrine symptoms should be managed. (1)

Outcomes
The general outcomes of interest are a change in disease status, functional outcomes, QOL, treatment-related mortality, and treatment-related morbidity. See Table 1 for the description and relevance of specific outcome measures considered in this policy.

As per the U.S. Food and Drug Administration (FDA) guidance document for developing drugs for the treatment of dystrophinopathies, the FDA has no defined set of required or recommended clinical outcome measures to be used in clinical studies. The guidance states that manufacturers should propose and, if necessary, develop endpoints that can validly and reliably assess patients with a wide spectrum of symptoms and disease stages. Further, it states, "The sponsor should include an assessment of multiple efficacy endpoints, when feasible, to characterize the breadth of effects on dystrophin-related pathologies, including skeletal, respiratory, and cardiac muscle function, even if the primary endpoint is only 1 of these measures." (6)

Table 1. Health Outcome Measures That May Be Relevant to Muscular Dystrophinopathies

Outcome Measure	Description	Scale	Clinically Meaningful Difference/Comment
Griffiths scale of mental development	Comprehensive, child friendly developmental measure for continuous use from birth to 6 years (72 months).	Consists of 2 sets of scales, 1 for each age group 0-2 years and 2-8 years.	Although used in Duchenne muscular dystrophy, this is a non-specific measure and its appropriateness to measure clinical efficacy for Duchenne muscular dystrophy has not been established.
Bayley scales of infant and toddler	Designed to assess developmental functioning from 1 month to 42 months	Composite scores are derived for cognitive, language, and motor development and	Although used in Duchenne muscular dystrophy, this is a non-specific measure

development (Third edition)	of age. Covers 5 domains: cognitive, language, motor, adaptive, and social emotional development.	scaled to a metric, with a mean of 100, standard deviation of 15, and range of 40 to 160.	and its appropriateness to measure clinical efficacy for Duchenne muscular dystrophy has not been established.
North Star Ambulatory Assessment (NSAA) or an age appropriate modified NSAA	Measures functional motor abilities. Appropriate for ambulatory children ages > 3 years of age with Duchenne muscular dystrophy.	17-item scale that grades each activity from 0 (unable to achieve independently) to 2 (normal- no obvious modification of activity). Scores can range from 0 to 34. Higher scores indicate improvement. Also includes recording timed items such as the 10-meter timed walk/run test and time to rise from the floor (Gower's test). These times are not included in the global score.	Not reported
6-minute walk test (6MWT) or shorter versions such as the 2-minute walk test	Measures strength and endurance and can be appropriate for patients as young as 5-6 years of age. Performance may increase with time in very young patients whereas performance tends to worsen with time in older patients. Floor effect of losing ambulation in older patients with more advanced disease and analyses of change in 6MWT can be strongly influenced by the inclusion or	Assesses distance walked in 6 minutes.	Estimates of minimum clinically important difference for Duchenne muscular dystrophy patients of a change of 30 meters have been reported. (7, 8) Interpretation of 6MWT results is limited by the variability in testing procedures and patient motivation.

	exclusion of patients who lose ambulation during the trial; such patients contribute zero values.		
Myometric assessments	Appropriate to measure increase or preserve muscle strength, and it can be used to provide reliable measurements in children ages 5 years and older.		Clinical meaningfulness of differences in muscle strength should be supported by the magnitude of the effect observed or by the demonstration of a drug effect on an appropriate functional measure.
Specific clinical respiratory outcomes	Nocturnal desaturation, aspiration pneumonia, and progression to mechanically assisted ventilation.	Varied outcome measure (dichotomous or continuous).	Clinical meaningfulness of differences should be supported by the magnitude of the effect observed or by the demonstration of a drug effect on an appropriate functional measure.
Biomarker (such as dystrophin)	Deficiency of functional dystrophin appears to be the proximate cause of the symptomatic and functional consequences of dystrophinopathies, justifying particular interest in dystrophin as a biomarker and as a potential surrogate endpoint for accelerated approval.	Dystrophin levels are measured in muscle fibers by immunohistochemical analysis to detect the presence or absence of dystrophin regardless of the actual quantity of dystrophin present while Western blot analysis quantifies the amount of dystrophin in the muscle tissue sample.	Dystrophin expression can only be viewed as supportive of the proof of principle. It is currently uncertain how predictive of sustained functional improvement the detected dystrophin level could be, and what levels may be required for a meaningful clinical improvement in Duchenne patients to be registered. Further, dystrophin produced by eteplirsen is an internally shortened protein and the clinical

			effect of the truncated dystrophin is still not fully known.

6MWT: 6-minute walk test; NSAA: North Star Ambulatory Assessment.

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.

The clinical development program of eteplirsen is summarized In Table 2. In addition, post-hoc analysis from these studies have also been published.

Table 2. Summary of the Clinical Development Program for Eteplirsen

Trial	NCT	Phase	Description	N	Design	Status
STUDY 201/202	NCT01396239	2	Treatment of ambulant subjects with Duchenne muscular dystrophy	12	DBRCT	Completed and published (9)
STUDY 204	NCT01540409	2	Rollover Study of Study 204 with a follow-up of 4 years	12	Open-label	Completed and published (10)
STUDY 301	NCT02255552 (PROMOVI)	3	Treatment of ambulant subjects aged 7 to 16 years with Duchenne muscular dystrophy	109	Open-label with concurrent untreated control arm	Completed and published (11)

DBRCT: double-blind randomized controlled trial; NCT: national clinical trial; NCT01396239: A Randomized, Double-Blind, Placebo-Controlled, Multiple Dose Efficacy, Safety, Tolerability and Pharmacokinetics Study of AVI-4658 (Eteplirsen), in the Treatment of Ambulant Subjects With Duchenne Muscular Dystrophy and Open-Label, Multiple-Dose, Efficacy, Safety, and Tolerability Study of Eteplirsen in Subjects With Duchenne Muscular Dystrophy Who Participated in Study 4658-US-201; NCT01540409: Open-Label, Multiple-Dose, Efficacy, Safety, and Tolerability Study of Eteplirsen in Subjects With Duchenne Muscular Dystrophy Who Participated in Study 4658-US-201; NCT02255552: An Open-Label,

Multi-Center, Study With a Concurrent Untreated Control Arm to Evaluate the Efficacy and Safety of Eteplirsen in Duchenne Muscular Dystrophy.

Randomized Controlled Trials

Study 201 is single-center, double-blind, placebo-controlled trial that randomized 12 males ages 7 to 13 years with Duchenne muscular dystrophy (DMD) amenable to exon 51 skipping and on stable corticosteroid dose for at least 6 months to eteplirsen (30 or 50 mg/kg/week) or placebo (4 participants per group) (Table 3).Treatment continued for 24 weeks and then placebo participants switched to eteplirsen 30 or 50 mg/kg (n=2 per group) at week 25. The primary trial endpoint was a measure of the change in dystrophin-positive fibers as measured in muscle biopsy tissue using immunohistochemistry. (4) 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. (9) 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 that 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. A more rigorous and fully blinded reanalysis of the FDA immunohistochemical assay by 3 investigators cast further doubt about the consistency of immunohistochemical analysis because there was little difference in positive fibers between original baseline samples and week 180. (13)

Observational Studies

Study 202 was a 4-year open-label trial that enrolled all patients from Study 201. The trial was designed to assess the ongoing efficacy and safety of eteplirsen. Individuals continued on the same dose of eteplirsen they received at the end of Study 201 (6 patients on 30 mg/kg and 6 patients on 50 mg/kg (Table 3). The prespecified clinical endpoints for the 6-minute walk test for study 201 (week 24) and study 202 (week 48) were negative. (13) The article reported a 67.3-meter benefit in the 6-minute walk test distance at week 48 in ambulation-evaluable eteplirsen-treated patients (n=6) compared with placebo/delayed patients ($p<0.005$). (9) However, this was a post-hoc analysis excluding 2 eteplirsen-treated patients who quickly deteriorated while receiving therapy and lost ambulation beginning at week 4 of the trial. The FDA has recommended retraction of the published study due to concerns about the interpretation of its findings. (14) Further, in an exploratory analysis, the FDA found no correlation between dystrophin levels and the 6-minute walk test distance. (13) For example, among the 4 patients with the most preserved 6-minute walk test, 2 had the lowest and 2 had the highest dystrophin levels as determined by Western blot. As per the prescribing label, there was no significant difference in change in 6-minute walk test distance between patients treated with eteplirsen and placebo. The use of the 6-minute walk test as an objective outcome instrument is limited by factors such as influence due to expectation bias, motivation, and coaching. Patients in the pivotal 201/202 trial were aware of treatment assignment for most of the investigation period.

McDonald et al. (2021) reported the results of the PROMOVI, an open-label study which enrolled 79 ambulatory participants aged 7 to 16 years with confirmed mutations amenable to exon 51 skipping. (11) These participants received the FDA approved dose of 30 mg/kg/week eteplirsen intravenously for 96 weeks. An untreated cohort with DMD not amenable to exon 51 skipping was also enrolled to serve as a control arm. Of the 79 participants enrolled in the eteplirsen cohort, 78 completed 96 weeks of treatment. In the untreated control arm, 15 of the 30 enrolled untreated participants completed the study. Post-hoc, authors deemed this control arm to be an inappropriate control group citing genotype-driven differences in clinical trajectory. Instead, the authors utilized post-hoc comparisons with participants from eteplirsen pivotal studies 201/202 and mutation-matched external natural history controls. Reported results showed attenuation of decline on the 6- minute walk test over 96 weeks (PROMOVI: -68.9 m; phase 2 studies (201/202) of eteplirsen: -67.3 m; external controls: -133.8 meters) and significant attenuation of percent predicted forced vital capacity annual decline (PROMOVI: -3.3%, phase 2 studies: -2.2%, external controls: -6.0%; p <.001). A comparison of clinical outcomes of eteplirsen-treated cohort with untreated cohort with DMD not amenable to exon 51 skipping was not reported.

Additional analysis reporting long-term data from studies 201/202 with multiple cutoffs dates reporting multiple clinical outcomes and their comparison with historical control has been published. These are summarized below. Interpretation of these results is confounded by unobserved or unadjusted baseline differences in prognostic variables between the groups.

Eteplirsen's manufacturer reported to the FDA Peripheral and Central Nervous System Drugs Advisory Committee meeting a gain of 162 meters on the 6-minute walk test at 4 years after treatment with eteplirsen in 12 patients in study 202 compared with 13 patients from an external control. (12) Results were subsequently published by Medell et al. (2016) (10) in a peer-reviewed journal. 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 6-minute walk test, age, and genotype amenable to exon 51 skipping therapy. However, the FDA (12) and others (15) 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.

Published studies suggest a linear annual decline of approximately 5% in the percent predicted forced vital capacity (FVC%) in patients with Duchenne muscular dystrophy, regardless of corticosteroid treatment. (16) Khan et al. (2019) summarized the mean annual decline in FVC% of eteplirsen-treated patients from studies 202 and 204, as well as interim results from 42 patients in study 301, and compared the results with a matched control group of glucocorticoid-treated Duchenne muscular dystrophy patients aged 10 to <18 years drawn from a registry with mutations amenable to exon 51 skipping (n=20). (17) Data on matched controls were obtained from prospective natural history studies of more than 400 Duchenne muscular dystrophy patients. (18) The data are summarized in Table 6. Compared to the matched control

group, eteplirsen-treated patients had a statistically significant slower decline in the annual rate of FVC%. Use of historical controls is problematic as the results are prone to bias, particularly if there is disease heterogeneity or change in diagnostic abilities or treatment standards over time. The above outcomes require careful evaluation and may not be appropriate evidence for evaluating a therapy even for an ultra-rare condition.

Kinane et al. (2018) reported long-term data (240 weeks or approximately 4.6 years) on pulmonary function outcomes of 12 participants from the pivotal study 201/202. (19) Results were compared with a historical natural cohort consisting of 34 participants who participated in the United Dystrophinopathy Project aged 7 to 15.5 years who had undergone pulmonary function testing. The annual decrease in FVC% in the eteplirsen and historical cohort was 2.3% (95% confidence interval [CI], 1.2% to 3.4%) and 4.1% (95% CI, 1.9% to 6.3%) respectively. Alfano et al. (2019) reported outcomes from the original cohort of 12 participants from the pivotal study 201/202. (20) It is unclear if the results of these studies provide any incremental information from the previously published studies that could meaningfully alter conclusions about the net health benefit of eteplirsen in participants with Duchenne muscular dystrophy amenable to exon 51 skipping.

Mitelman et al. (2022) reported analysis of 12 participants from study 201/202 with a median follow-up of approximately 6 years of eteplirsen treatment. (21) Outcomes included loss of ambulation and FVC%. Outcomes were compared between eteplirsen-treated participants and historical external controls. Compared to historical controls, eteplirsen-treated participants experienced a statistically significant longer median time to loss of ambulation by 2.09 years (5.09 vs. 3.00 years, p <.01) and significantly attenuated rates of pulmonary decline versus historical control (FVC % change: -3.3 vs. -6.0 percentage points annually, p <.0001).

Safety

The majority of adverse events observed in the clinical trials of eteplirsen were considered to be mild or moderate. Overall, 8 severe adverse events (incision site hemorrhage, hemorrhoids, back pain, cardiomyopathy, nasal congestion, balance disorder, bone pain, and femur fracture) were observed during the clinical trial program of eteplirsen. Except for the cardiomyopathy, which occurred during a dose-ranging trial of eteplirsen, all were considered not to be related to the use of eteplirsen. (12)

Table 3. Summary of Key Study Characteristics

Study; Trial	**Country**	**Design**	**Sites**	**Duration**	**Participants**	**Interventions**	
						Active	Comparator
Study 201							
Mendell et al. (2013) (9)	U.S.	RCT	1	24 weeks	Patients with Duchenne muscular dystrophy ages	eteplirsen 30mg/kg/ week (n=4); eteplirsen 50	Placebo (n=4)

					7-13 years with confirmed deletions amenable to skipping exon 51 and ability to walk 200-400 m on 6MWT and on glucocorticoids for ≥24 weeks.	mg/kg/week (n=4)	
Study 202							
Mendell et al. (2016) (10)	U.S.	Open label	1	4 years	All patients from study 201 were enrolled in study 202.	eteplirsen 30 mg/kg/week (n=6); eteplirsen 50 mg/kg/week (n=6)	None
Study 301							
Khan et al. (2019) (17)	U.S.	Open label, ongoing study[a]	37	96 weeks	Patients with Duchenne muscular dystrophy ages 7-16 years with confirmed deletions amenable to skipping exon 51 and ability to walk >300 m on 6MWT and on glucocorticoids for ≥24 weeks.	Eteplirsen 30 mg/kg/week (n=12); target is 80 participants	Untreated controls of patients with Duchenne muscular dystrophy not amenable to exon 51 skipping

RCT: randomized controlled trial; 6MWT: 6-minute walk test; U.S.: United States; yrs: years;
[a] This study was ongoing at the time of publication of this paper (PROMOVI; NCT02255552). The FDA asked Sarepta for additional data for review and Sarepta provided information on 13 individuals currently enrolled in the PROMOVI trial who had baseline and 48-week data.

Table 4. Summary of Pivotal Trial 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) (9)					
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
	Mean Percent Normal Dystrophin (SD)				
	Baseline		Week 48	p	
Sarepta et al. (2016)	0.16 (0.12)		0.44 (0.43)	0.008	

6MWT: 6-minute walk test; mg:milligram; NR: not reported; SD: standard deviation; SE: standard error;
[a] p<0.01 vs. baseline
[b] Excluding 2 individuals who showed rapid disease progression at week 4 of study.
[c] p<0.001 vs. delayed eteplirsen group.

Table 5. Summary of Pivotal Trial Results (Functional Outcomes) Compared to Historical Controls

	6MWT, mean meters (SD)					Loss of Ambulation, n (%)				
	Baseline	Year 1	Year 2	Year 3	Year 4	Baseline	Year 1	Year 2	Year 3	Year 4
Mendell et al. (2016) (10)										
Eteplirsen (n=12)	363.2 (42.2)	305.8 (155.3)	295.9 (149.0)	263.1 (151.7)	196.3 (130.2)	All ambulatory	2 (17)	2 (17)	2 (17)	2 (17)
External control (n=13)[a]	257.6 (66.8)	318.6 (94.2)	223.5 (145.4)	110.3 (136.2)	27.3 (90.3)	-	All ambulatory	3 (23)	6 (46)	10 (77)

Adapted from The Institute for Clinical and Economic Review Evidence Report.
6MWT: 6-minute Walk Test; SD: standard deviation.
[a] Two historical control patients did not have data at all time points; 1 contributed until year 1, and the second contributed until year 2.

Table 6. Summary of Key Study Results (Pulmonary Outcomes) Using Historical Controls

Matched Control/Trials (18)	Number of observations	Baseline Mean	Mean Annual Change (SE) in FVC%	Difference in Annual Change Versus	P-value

				Control, 95% CI	
Matched Control (n=20)	88	79.6 (13.3)	-6.00 (0.41)	Reference	-
Study 201/202 (n=12)	132	96.9 (14.0)	-2.19 (0.71)	3.81 (2.19 to 5.42)	<0.001
Study 204 (n=20)	117	65.9 (16.6)	-3.66 (0.68)	2.34 (0.77 to 3.90)	0.004
Study 301 (n=42)	184	78.5 (15.7)	-3.79 (0.82)	2.21	0.017

Adapted from The Institute for Clinical and Economic Review Evidence Report; CI: confidence interval; FVC%: percent predicted forced vital capacity; n: number; SE: standard error.

The purpose of limitations tables (Tables 7 and 8) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides conclusions on the sufficiency of the evidence supporting the position statement.

Table 7. Study Relevance Limitations

Study; Trial	**Population[a]**	**Intervention[b]**	**Comparator[c]**	**Outcomes[d]**	**Follow-Up[e]**
Mendell et al. (2013) (9) Study 201				2. Primary endpoint was physiologic measure (dystrophin level) and correlation with clinical benefit is unknown 4. Dystrophin measured by IHC staining which only reports presence or absence, verses Western blot which measures quantity of dystrophin 6. Clinical significant difference not supported.	
Mendell et al. (2016) (10) Study 202				5. Clinical significant difference for 6MWT was not pre-specified 6. Clinical significant difference not supported.	

Khan et al. (2019) (17) Study 301				5. Clinical significant difference for percent predicted forced vital capacity was not pre-specified 6. Clinical significant difference not supported.	

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.
6MWT: 6-minute Walk Test; 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 8. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Mendell et al. (2013) (9) Study 201	3. No description of randomization procedure or subsequent concealment	1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician		5. Inappropriate exclusions (2 of 8 patients in treatment arms who lost ambulation were excluded from 6MWT analysis)	1.Small sample size (each arm had 4 participants)	
Mendell et al. (2016) (10) Study 202	1. Participants not randomly allocated 4. Inadequate control for selection bias.	1. Not blinded to treatment assignment			1.Small sample size (arms had 2 or 4 patients)	

		2. Not blinded outcome assessment 3. Outcome assessed by treating physician				
Khan et al. (2019) (17) Study 301	1. Participants not randomly allocated 4. Inadequate control for selection bias.	1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician		1. High loss to follow-up or missing data (preliminary results of an ongoing study-results from 42 of an expected 109 participants)		

The study limitations stated in this table are those notable in the current policy; this is not a comprehensive gaps assessment. 6MWT: 6-minute Walk Test;

[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 differences.

[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.

Section Summary: Eteplirsen for Treatment of Duchenne Muscular Dystrophy

Evidence for the use of eteplirsen for the treatment of Duchenne muscular dystrophy amenable to exon 51 skipping includes a single RCT and an ongoing prospective open-label trial with a concurrent untreated control arm. In addition, multiple post-hoc studies with longer follow-up

and use of historical comparators have also been published. For the single pivotal RCT, no formal sample size calculations were conducted. A sample size of 12 total participants was selected with 4 participants in 3 treatment groups. There was no statistically significant difference either in the mean change from baseline in 6-minute walk test distance or change in North Star Ambulatory Assessment total score between eteplirsen-treated participants and placebo-treated participants at week 48. While eteplirsen treatment resulted in dystrophin detection in muscle biopsies suggesting the production of (truncated) dystrophin, the amount of protein produced was very limited according to the Western blot results (0.44% of normal dystrophin at week 48 [Study 301]; 0.93% at week 180 [Study 201/202]). There are no satisfactory data, clearly establishing the effectiveness of the truncated dystrophin. Further, the minimum beneficial amount of dystrophin expression to be translated into a clinical benefit has yet to be established. In the absence of clinical data convincingly demonstrating a clinical effect, it cannot be concluded that the amount of dystrophin expressed with eteplirsen will translate into a clinical benefit to patients. Multiple analyses of long-term follow-up data from study 201/202 and 301 on functional outcome measures such as 6-minute walk test and pulmonary function suggest that the rate of decline in eteplirsen- treated participants was less as compared to historical controls. However, the post-hoc nature of the analysis and the fact that the cohorts were retrospectively identified within the untreated group of participants is of serious concern due to potential selection bias and undermines the robustness of the data. Particularly, the 6- minute walk test is subject to inter- and intra-subject variability and is influenced by training and motivation making it a less suitable outcome measure for external control group comparison. Thus, the clinical benefit of treating Duchenne muscular dystrophy with eteplirsen, including improved motor function and pulmonary function, has not been demonstrated. A confirmatory, prospective and adequately powered trial is necessary to assess the net health benefit of eteplirsen in patients with Duchenne muscular dystrophy amenable to 51 skipping.

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 1 randomized controlled trial (RCT), 1 ongoing prospective open-label trial with a concurrent untreated control arm, and multiple post-hoc studies with historical controls. Relevant outcomes are disease-specific survival, change in disease status, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. For the single pivotal RCT, no formal sample size calculations were conducted. A sample size of 12 total patients was selected with 4 patients in 3 treatment groups. There was no statistically significant difference either in the mean change from baseline in the 6-minute walk test distance or change in the North Star Ambulatory Assessment (NSAA) total score between eteplirsen treated patients and placebo treated patients at week 48. While eteplirsen treatment resulted in dystrophin detection in muscle biopsies suggesting the production of (truncated) dystrophin, the amount of protein produced was very limited according to the Western blot results (0.44% of normal dystrophin at week 48 [Study 301]; 0.93% at week 180 [Study 201/202]). There are no satisfactory data, clearly establishing the effectiveness of the truncated dystrophin. Further, the minimum beneficial amount of dystrophin expression to be translated into a clinical benefit has yet to be

established. In the absence of clinical data convincingly demonstrating a clinical effect, it cannot be concluded that the amount of dystrophin expressed with eteplirsen will translate into a clinical benefit to patients. Multiple analyses of long-term follow-up data from study 201/202 and 301 on functional outcome measures such as 6-minute walk test and pulmonary function suggest that the rate of decline in eteplirsen treated patients was less as compared to historical controls. However, the post-hoc nature of the analyses and the fact that the cohorts were retrospectively identified within the untreated group of participants is of serious concern due to potential selection bias and undermines the robustness of the data. Particularly, the 6-minute walk test is subject to inter- and intra-subject variability and is influenced by training and motivation making it a less suitable outcome measure for external control group comparison. Thus, the clinical benefit of treating Duchenne muscular dystrophy with eteplirsen, including improved motor function and pulmonary function, has not been demonstrated. A confirmatory, prospective and adequately powered trial is necessary to assess the net health benefit of eteplirsen in patients with Duchenne muscular dystrophy amenable to 51 skipping. Based on available data, eteplirsen for the treatment of Duchenne muscular dystrophy is considered not medically necessary as a clinical benefit has not been established. The use of Eteplirsen for the treatment of all other indications is considered experimental, investigational and/or unproven as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

Centers for Disease Control and Prevention

In 2010, the U.S. Centers for Disease Control and Prevention convened a Duchenne muscular dystrophy Care Considerations Working Group. In 2010, the Working Group developed care recommendations (6), and updated them in 2018. (26) Their 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. The Working Group did not make recommendations on the use of eteplirsen. However, eteplirsen is discussed briefly under the section on “Emerging treatments.” (27), In 2016, the Working Group stated that eteplirsen was approved by the U.S. Food and Drug Administration (FDA) for males with the dystrophin gene variant amenable to exon 51 skipping, which is about 13% of the males with Duchenne muscular dystrophy.

American Heart Association

In 2017, a statement from the American Heart Association addressed the treatment of cardiac issues in individuals with any of several neuromuscular diseases, including Duchenne muscular dystrophy. (28) 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 co-authors disclosed being an industry-supported investigator for the drug.

American Academy of Neurology

In 2016, the American Academy of Neurology published an updated practice guideline on the use of corticosteroids for the treatment of Duchenne muscular dystrophy. (29) The Academy does not discuss the use of eteplirsen for Duchenne muscular dystrophy.

Institute for Clinical and Economic Review

The Institute for Clinical and Economic Review (16) concludes, "Data on patient-important outcomes with eteplirsen are extremely limited, and studies of dystrophin levels show increases that are of uncertain clinical/biologic importance. There is no high- or moderate quality evidence demonstrating improvements in function with eteplirsen, as the available long-term data showing potential clinical benefits are observational with matched or historical controls and need to be confirmed in larger, ongoing trials. Furthermore, the main outcome reported, 6-minute walk test, is subject to patient effort, which may lead to less precision in the outcome measure and affect the results of a small, unblinded study. There are no particularly concerning safety signals with eteplirsen but given the small number of patients and short follow-up times, harms could be missed. We consider the evidence to be insufficient ("I"), as certainty of net benefit based on currently available evidence is low."

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 9.

Table 9. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03992430[a]	A Study to Compare Safety and Efficacy of a High Dose of Eteplirsen in Duchenne Muscular Dystrophy (DMD) Patients (MIS51ON)	154	Nov 2024
Unpublished			
NCT02420379[a]	An Open-Label, Multi-Center Study to Evaluate the Safety, Efficacy, and Tolerability of Eteplirsen in Early Stage Duchenne Muscular Dystrophy	33	Dec 2018
NCT02255552[a]	Study of Eteplirsen in DMD Patients (PROMOVI)	109	Jul 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	Mar 2021

NCT: national clinical trial.

[a] Denotes industry sponsorship or co-sponsorship

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J1428

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
09/15/2024	Reviewed. No changes.
10/15/2023	Document updated with literature review. Coverage unchanged. Added references 11, 21-25; others updated and/or removed.
01/01/2023	Reviewed. No changes.
01/01/2022	Document updated with literature review. Coverage unchanged. Added references 17, 23; others updated.
07/01/2020	Document updated with literature review. Coverage unchanged. The following references were added 6, 7, 8, 11, 17-26. Title changed from “Eteplirsen (Exondys 51)”
04/15/2018	Reviewed. No changes.
06/15/2017	New medical document. Eteplirsen (Exondys 51™) for the treatment of Duchenne muscular dystrophy is considered not medically necessary as a clinical benefit has not been established. Eteplirsen (Exondys 51™) for the

	treatment of all other indications is considered experimental, investigational and/or unproven.