Exondys 51® (Eteplirsen)

Policy Number: 2025D0058N
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➲ Instructions for Use

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Coverage Rationale

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Exondys 51® (eteplirsen) may be covered for the treatment of Duchenne muscular dystrophy (DMD) in patients who meet all of the following criteria:

Initial Therapy

- Diagnosis of Duchenne muscular dystrophy by, or in consultation with, a neurologist with expertise in the diagnosis of DMD; **and**
- Submission of medical records (e.g., chart notes, laboratory values) confirming the mutation of the DMD gene is amenable to exon 51 skipping; **and**
- **One** of the following:
  - Submission of medical records (e.g., chart notes, laboratory values) confirming that the patient has a 6-Minute Walk Test (6MWT) ≥ 300 meters while walking independently (e.g., without side-by-side assist, cane, walker, wheelchair, etc.) prior to beginning Exondys 51 therapy; **or**
  - **Both** of the following:
    - Submission of medical records (e.g., chart notes) confirming that the patient is ambulatory **without** needing an assistive device (e.g., without side-by-side assist, cane, walker, wheelchair, etc.); **and**
    - **One** of the following:
      - Patient has achieved a score of greater than 17 on the North Star Ambulatory Assessment (NSAA); **or**
      - Patient has achieved a time to rise (TTR) of less than 7 seconds

  and
- **One** of the following:
  - Patient has not previously received gene therapy [e.g., Elevidys (delandistrogene moxparvovec-rokl)] for the treatment of DMD; **or**
  - **Both** of the following:
    - Patient has previously received gene therapy [e.g., Elevidys (delandistrogene moxparvovec-rokl)] for the treatment of DMD; **and**
    - Submission of medical records (e.g., chart notes, laboratory values) documenting a clinically meaningful functional decline resulting from loss of muscle strength/motor ability (e.g., loss of a motor milestone) since receiving gene replacement therapy [e.g., Elevidys (delandistrogene moxparvovec-rokl)]

  and
- Exondys 51 is not used concomitantly with other exon skipping therapies for DMD [e.g., Amondys (casimersen), Viltepso (viltolarsen), Vyondys 53 (golodirsen)]; **and**

- Exondys 51 is prescribed by, or in consultation with, a neurologist with expertise in the treatment of DMD; **and**
- Dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
- Initial authorization will be for no more than 12 months

Continuation Therapy

- Submission of medical records (e.g., chart notes) confirming that the patient is ambulatory **without** needing an assistive device (e.g., without side-by-side assist, cane, walker, wheelchair, etc.); **and**
- Exondys 51 is not used concomitantly with other exon skipping therapies for DMD [e.g., Amondys (casimersen), Viltepso (viltolarsen), Vyondys 53 (golodirsen)]; **and**
- Prescribed by, or in consultation with, a neurologist with expertise in the treatment of DMD; **and**
- Dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
- Reauthorization will be for no more than 12 months

Unproven

Exondys 51 is unproven and not medically necessary for the treatment of other forms of muscular dystrophy (e.g., Becker muscular dystrophy).

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J1428	Injection, eteplirsen, 10 mg

Diagnosis Code	Description
G71.01	Duchenne or Becker muscular dystrophy

Background

Duchenne muscular dystrophy (DMD) is an X-linked disease that affects 1 in 3,500 to 5,000 live male births. DMD occurs as a result of mutations (mainly deletions) in the dystrophin gene. These mutations lead to an absence or a defect of the protein, dystrophin, resulting in progressive muscle degeneration, leading to loss of ambulation by age 8-14 years, and ultimately life-threatening complications including cardiomyopathy and respiratory insufficiency.

Eteplirsen is an antisense oligonucleotide designed to bind to exon 51 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 51 skipping. Approximately 13% of DMD patients have out of frame deletion mutations amenable to exon 51 skipping. Exon skipping is intended to allow for production of an internally truncated dystrophin protein.

Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy.

Clinical Evidence

Eteplirsen is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

Mendell et al (2013) evaluated eteplirsen for the treatment of DMD in a small (n = 12), randomized, multi-center, double-blind, placebo-controlled study, receiving weekly infusions of either placebo, eteplirsen 30 mg/kg or eteplirsen 50 mg/kg for 24 weeks.[1,6] Following the 24-week study, placebo/delayed patients switched to an open-label extension treatment (Mendell 2016) with either dosing of eteplirsen regimen.[8] Outcome measures assessed the primary outcome of eteplirsen-induced dystrophin production, as well as the 6-minute walk test (6MWT, reported as 6-minute walk distance, 6MWD). Patients had a mean age of 9.4 years, and a mean 6MWD at baseline of 363 meters, and were on a stable dose of corticosteroids for at least 6 months. The patients participating in the extension study were compared to an external natural history control group. At 180 weeks of treatment, eleven patients underwent a muscle biopsy to analyze for dystrophin protein. The average dystrophin protein level after 180 weeks of treatment was 0.93% of the dystrophin level in healthy subjects. At week 24, the 30 mg/kg eteplirsen patients were biopsied, and percentage of dystrophin-positive fibers increased to 23% of normal vs. placebo ($p \leq 0.002$). At week 48, there was a 52% and 43% increase (in the 30 and 50 mg/kg/wk cohorts, respectively), which suggests that dystrophin increases with longer treatment. Restoration of function dystrophin was confirmed by detection of sarcoglycans and neuronal nitric oxide synthase at the sarcolemma. Ambulation-evaluable eteplirsen-treated patients experienced a 67.3 meter benefit compared to placebo patients ($p \leq 0.001$). The investigators concluded that eteplirsen restored dystrophin in the 30 and 50 mg/kg/wk cohorts, and in subsequently treated placebo subjects. According to the prescribing information, however, this study failed to provide evidence of a clinical benefit of eteplirsen.

Kinane et al (2018) evaluated eteplirsen on its impact on the lung function of DMD patients who received treatment in the eteplirsen studies 201 and 202. Studies 201/202 included 12 patients treated with eteplirsen over 5 years.[9] These studies did not have an active placebo control and relied on a natural history control from the United Dystrophinopathy Project (UDP) and published natural history. The investigators measured forced vital capacity (FVC), maximum expiratory pressure (MEP), and maximum inspiratory pressure (MIP). The experimental patient FVC values were compared to the UDP data, however MEP and MIP were compared to published natural history. Pulmonary function tests (PFTs) were performed by experienced physical therapists who were trained in performing spirometry in compliance with ATS/ERS guidelines. This data was comparted to patient-level data from 34 patients who participated in the UDP, whose age range was similar to that of the experimental group. Prospective spirometry data was collected by the UDP in compliance with ATS/ERS guidelines. Only FVC and FVC% predicted were assessed, while MIP and MEP were not. An age-adjusted mixed-effects analysis was used to evaluate the experimental group against the natural history cohort from the UDP. The investigators plotted the datapoints of FVC and FVC%p of the eteplirsen-treated patients and compared to the natural history cohorts. The data showed the slope of the decline in FVC%p was -4.1 for the natural history cohort vs. -2.3 for the eteplirsen-treated group. There were no comparisons of MEP and MIP between the two groups. The authors suggest, comparing to published literature that the annual decline in MEP%p for eteplirsen-treated patients of 2.6% is comparable to slightly lower than the decline of 2.7% to 3.6% observed in published reports of DMD patients. The annual increase in MIP%p of 0.6% per year compares favorably to what has been observed and published historically (3.8% to 3.9%). The investigators concluded that with eteplirsen treatment, deterioration of respiratory muscle function, based on PFTs, was less than that seen in the UDP group or compared favorably with natural history. The 201/202 studies did not take into consideration intrasubject variability and did not include a placebo group for direct comparison, relying solely on natural history or historical cohort control, which occurred as late as a decade prior (2005) to these studies. Robust clinical information regarding the historical controls was not disclosed, which could include genetics, age, time to first treatment, standard of care, etc. According to the prescribing information, however, the 201/202 studies failed to provide evidence of a clinical benefit of eteplirsen.

In 2021, McDonald et al published the results of PROMOVI, a 96-week, multicenter, open-label, non-randomized trial evaluating the efficacy and safety of eteplirsen in patients with DMD and genetic deletions amenable to exon 51 skipping, with an intended control group of patients with DMD and genetic deletions not amenable to exon 51 skipping. Eligible patients were male, aged 7–16 years, with DMD and genotypically confirmed mutations amenable to exon 51 skipping (eteplirsen-treated group) or with genotypically confirmed mutations not amenable to exon 51 skipping (untreated control group). Patients were required to have stable pulmonary function (percent predicted forced vital capacity [FVC%p] ≥ 50%, not requiring nocturnal ventilation, and unlikely to decompensate over the duration of the study), be on a stable dose of oral corticosteroids for at least 24 weeks before study entry and be able to walk ≥ 300 m on the 6-minute walk test (6MWT).

Patients in the treated group received a weekly intravenous (IV) infusion of 30 mg/kg eteplirsen, administered over approximately 35–60 minutes, from baseline (Week 1) until the end of the study (Week 96). The primary efficacy endpoint was the change from baseline to Week 96 in 6MWT distance. Secondary efficacy endpoints included change from baseline to Week 96 for the ability to rise independently from the floor, LOA, NSAA total score, and FVC%p. Post-hoc analyses were performed with genotype- and baseline characteristic-matched comparisons of a subset of PROMOVI data with external natural history control cohorts and data from previous eteplirsen phase 2 studies.

Seventy-eight out of 79 eteplirsen-treated patients completed 96 weeks of treatment. Fifteen out of 30 untreated patients completed the study; this cohort was considered an inappropriate control group because of genotype-driven differences in clinical trajectory. At Week 96, eteplirsen-treated patients showed increased exon skipping (18.7-fold; $p < 0.001$) and dystrophin protein (7-fold; $p > 0.001$) versus baseline. Mean 6MWT distance decreased from 374.6m at baseline to 256.2m at Week 96. At Week 96, 54.1% of eteplirsen-treated patients were able to rise from the floor independently compared with 86.6% at baseline. The Kaplan-Meier estimate for remaining ambulatory at Week 96 was 81.9%; LOA occurred in 17.9% of eteplirsen-treated patients. The NSAA total score for eteplirsen-treated patients was 14.9 at Week 96 compared with 21.4 at baseline. Mean FVC% p decreased from 90.4% at baseline to 87.3% at Week 96. Post-hoc comparisons with patients from eteplirsen phase 2 studies and mutation-matched external natural history controls confirmed previous results, suggesting clinically notable attenuation of decline on the 6-minute walk test over 96 weeks (PROMOVI: -68.9 m; phase 2 studies: -67.3 m; external controls: -133.8 m) and significant attenuation of percent predicted forced vital capacity annual decline (PROMOVI: -3.3%, phase 2 studies: -2.2%, external controls: -6.0%; $p < 0.001$). Adverse events were generally mild to moderate and unrelated to eteplirsen. Most frequent treatment-related adverse events were headache and vomiting; none led to treatment discontinuation.

Eteplirsen has not been studied in DMD that is not amenable to exon 51 skipping, nor in other forms of muscular dystrophy (e.g., Becker muscular dystrophy).

Institute for Clinical and Economic Review (ICER)

On April 22, 2022, the Institute for Clinical and Economic Review (ICER) released a clinical report entitled, “Deflazacort, eteplirsen, and golodirsen for Duchenne muscular dystrophy: effectiveness and value.” In this report, ICER concluded that data for eteplirsen and golodirsen to be insufficient. Data on the exon-skipping drugs is extremely limited and randomized trial benefits are limited to the surrogate outcome of dystrophin levels. The small increases in dystrophin levels seen in the random controlled trials are of uncertain clinical significance. Observational studies comparing outcomes with historical controls have suggested potential functional benefits with eteplirsen, but these data may be confounded and effort dependent. Based on the current evidence, there are no particularly concerning safety issues with either drug, but given the small numbers of patients and limited follow-up, harms could be missed.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Exondys 51 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with Exondys 51. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

References

1. Exondys 51 [package insert]. Cambridge, MA: Sarepta Therapeutics, Inc.; December 2024.
2. Mendell JR, Rodino-Klapac LR, Sahenk Z, et al. Eteplirsen for the treatment of Duchenne muscular dystrophy. Ann Neurol. 2013 Nov;74(5):637-47.
3. Mendell JR, Goemans N, Lowes LP, et al. Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy. Ann Neurol. 2016 Feb;79(2):257-71.
4. Kinane TB, Mayer OH, Duda PW, et al. Long-Term Pulmonary Function in Duchenne Muscular Dystrophy: Comparison of Eteplirsen-Treated Patients to Natural History. J Neuromuscul Dis. 2018;5(1):47-58.
5. McDonald CM, Shieh PB, Abdel-Hamid HZ, et al. Open-Label Evaluation of Eteplirsen in Patients with Duchenne Muscular Dystrophy Amenable to Exon 51 Skipping: PROMOVI Trial. J Neuromuscul Dis. 2021;8(6):989-1001.
6. Institute for Clinical and Economic Review (ICER). Deflazacort, eteplirsen, and golodirsen for Duchenne muscular dystrophy: Effectiveness and value: Evidence Report. ICER_DMD-Final-Report_081519-2.pdf. April 22, 2022. Accessed February 7, 2025.

Policy History/Revision Information

Date	Summary of Changes

07/01/2025	**Coverage Rationale**
	• Revised coverage criteria for initial therapy; added criterion requiring **one** of the following:
	  ○ The patient has not previously received gene therapy [e.g., Elevidys (delandistrogene moxparvovec-rokl)] for the treatment of Duchenne muscular dystrophy (DMD)
	  ○ **Both** of the following:
	  ▪ Patient has previously received gene therapy [e.g., Elevidys (delandistrogene moxparvovec-rokl)] for the treatment of DMD
	  ▪ Submission of medical records (e.g., chart notes, laboratory values) documenting a clinically meaningful functional decline resulting from loss of muscle strength/motor ability (e.g., loss of a motor milestone) since receiving gene replacement therapy [e.g., Elevidys (delandistrogene moxparvovec-rokl)]
	Supporting Information
	• Updated *Benefit Considerations* section to reflect the most current information
	• Archived previous policy version 2025D0058M

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.