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Policy Number: 034.003

Title: Coverage Determination Policy for Exondys 51 (Eteplirsen)

Regions: ☒ **Texas** ☐ **Florida** ☐ **Indiana** ☐ **New Jersey** ☒ **New Mexico**

Impacted Areas:

- ☒ Network Management/Provider Services
- ☐ Member services
- ☐ Quality Management
- ☐ Credentialing
- ☐ IT
- ☐ Administration
- ☐ Compliance/delegation
- ☒ Utilization Management
- ☐ Case management
- ☐ Disease management
- ☒ Claims
- ☐ Human resources
- ☐ Finance
- ☒ Pharmacy
- ☐ ALL

Available LCD/NCD/LCA: None

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Coverage Policy Number: 034.003

Line of Business: Medicare Part B

Policy Type: Prior Authorization

Coverage Determination:

Initial/New Requests

Exondys 51 (Eteplirsen) is proven and medically necessary for the treatment of:

Duchenne Muscular Dystrophy (DMD), in patients with confirmed mutation of the Duchenne Muscular Dystrophy gene that is amenable to exon 51 skipping when **ALL** of the following criteria are met:

A. Diagnosis of Duchenne muscular dystrophy by, or in consultation with a neurologist with expertise in the diagnosis of DMD

B. Submission of medical records (e.g., chart notes, laboratory values) confirming the mutation of the DMD gene is amenable to exon 51 skipping; and

C. **ONE** of the following:

I. 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

II. BOTH of the following:

a. 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

b. ONE of the following:

i. Patient has achieved a score of greater than 17 on the North Star Ambulatory Assessment (NSAA); or

ii. Patient has achieved a time to rise from the floor (Gower's test) of less than 7 seconds

D. Exondys 51 is prescribed by, or in consultation with, a neurologist with expertise in the treatment of DMD

E. Exondys 51 is not used concomitantly with other exon skipping therapies for DMD (e.g., Vyondys 53)

F. Exondys 51 dosing for DMD is in accordance with the United States Food and Drug Adminstration approved labeling

G. Initial authorization will be for no more than 6 months

Note: Exondys 51 will not be approved for other forms of muscular dystrophy

Renewal/Continuation of Therapy Requests

For continuation of therapy, **ALL** of the following:

A. 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.)

B. Exondys 51 dosing for DMD is in accordance with the United States Food and Drug Administration approved labeling

C. Exondys 51 is prescribed by, or in consultation with, a neurologist with expertise in the treatment of DMD

D. Exondys 51 is not used concomitantly with other exon skipping therapies for DMD (e.g., Vyondys 53).

E. Reauthorization will be for no more than 12months

FDA Approved Dose and Indication

FDA Approved Indication	Approved Dosing
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	30 mg/kg IV infusion once weekly administered over 35 to 60 minutes

NOTE:

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.

General Background

Duchenne muscular dystrophy (DMD) is an X-linked disease that affects 1 in 3,600 – 6,000 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 and additional respiratory, orthopedic, and cardiac complications. If left untreated, mean age of death is approximately 19 years of age.

Exondys 51® (eteplirsen) is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) subclass. PMOs are synthetic molecules in which the five-membered ribofuranosyl rings found in natural DNA and RNA are replaced by a six-membered morpholino ring. Each morpholino ring is linked through an uncharged phosphorodiamidate moiety rather than the negatively charged phosphate linkage that is present in natural DNA and RNA. Each phosphorodiamidate morpholino subunit contains one of the heterocyclic bases found in DNA (adenine, cytosine, guanine, or thymine). Eteplirsen contains 30 linked subunits.

Eteplirsen is 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. Exon skipping is intended to allow for production of an internally truncated dystrophin protein.

Warning and Precautions:

Hypersensitivity Reactions: Hypersensitivity reactions, including bronchospasm, chest pain, cough, tachycardia, and urticaria, have occurred in patients treated with Exondys 51. If hypersensitivity reactions occur, institute appropriate medical treatment and consider slowing infusion or interrupting therapy.

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.

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. 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 Exondys 51® (Eteplirsen) Page 3 of 4 UnitedHealthcare Commercial Medical Benefit Drug Policy Effective 04/01/2021 Proprietary Information of UnitedHealthcare. Copyright 2021 United HealthCare Services, Inc. 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 soley 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.

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. Following the 24-week study, placebo/delayed patients switched to an open-label extension treatment (Mendell 2016) with either dosing of eteplirsen regimen. 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 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.

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).

HCPCS Code

HCPCS Code	Description
J1428	eteplirsen 10 mg; available as a 50 MG/1 ML Intravenous Solution

Acronyms

DMD = Duchenne Muscular Dystrophy

NCD = National Coverage Determination

LCD = Local Coverage Determination

6MWT = 6-Minute Walk Test

NSAA = North Star Ambulatory Assessment

PMO = Phosphorodiamidate Morpholino Oligomer

FVC = Forced Vital Capacity

MEP = Maximum Expiratory Pressure

MIP = Maximum Inspiratory Pressure

PFT = Pulmonary Function Test

UDP = United Dystrophinopathy Project

ATS = American Thoracic Society

ERS = European Respiratory Society

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