Exondys 51® (Eteplirsen) (for Pennsylvania Only)

Policy Number: CSPA2024D0058J
Effective Date: August 1, 2024

➲ Instructions for Use

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Related Policies
None

Application

This Medical Benefit Drug Policy only applies to the state of Pennsylvania.

Coverage Rationale

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

- For **initial therapy**, all of the following:
  - 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;[1,2]; **and**
  - **One** of the following:
    - Submission of medical records documenting a baseline evaluation, including a standardized assessment of motor function by a neurologist with experience in treating Duchenne muscular dystrophy, 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 from the floor (Gower's test) of less than 7 seconds; **and**
  - Exondys 51 is prescribed by, or in consultation with, a neurologist with expertise in the treatment of DMD; **and**
  - Exondys 51 dosing for DMD is in accordance with the United States Food and Drug Administration approved labeling; **and**
  - Exondys 51 is not used concomitantly with other exon skipping therapies for DMD (e.g., Vyondys 53); **and**
  - Initial authorization will be for 12 months
- For **continuation therapy**, all of the following:
  - Exondys 51 is prescribed by, or in consultation with, a neurologist with expertise in the treatment of DMD; **and**
  - Documentation of continued clinical benefit based on prescriber's assessment, including an evaluation with a standardized assessment of motor function ability by a neurologist with experience in treating Duchenne muscular dystrophy; **and**

- Exondys 51 dosing for DMD is in accordance with the United States Food and Drug Administration approved labeling; **and**
- Exondys 51 is not used concomitantly with other exon skipping therapies for DMD (e.g., Vyondys 53); **and**
- Reauthorization will be for no more than 12 months

Exondys 51 will not be covered for other forms of muscular dystrophy.[1]

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 federal, state, or contractual requirements 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 3,600–6,000 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.[3-4]

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.[1]

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. 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.[1]

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.[1]

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.

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.

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).[1]

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.[1]

References

1. Exondys 51 [package insert]. Cambridge, MA: Sarepta Therapeutics, Inc, January 2022.
2. Anthony K, Feng L, Arechavala-Gomeza V, et al. Exon skipping quantification by quantitative reverse-transcription polymerase chain reaction in Duchenne muscular dystrophy patients treated with the antisense oligomer eteplirsen. Hum Gene Ther Methods. 2012 Oct;23(5):336-45.
3. Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, Cripe L, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol; 2010 Jan; 9(1):77-93.
4. Bushby K, Finkel R, Birnkrant DJ, et al. (2010) Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care. Lancet Neurol; 2010 Jan; 9(2):177-189.
5. Gold Standard, Inc. Exondys 51. Clinical Pharmacology [database online]. Available at: https://www.clinicalkey.com/pharmacology/. Accessed January 30, 2024.
6. 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.

7. Sarepta Therapeutics. Confirmatory Study of Eteplirsen in DMD Patients (PROMOVI). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2017 Jan 27]. Available from: https://clinicaltrials.gov/show/NCT02255552. NLM Identifier: NCT 02255552.
8. 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.
9. 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.

Policy History/Revision Information

Date	Summary of Changes
08/01/2024	**Coverage Rationale** • Changed duration for initial authorization from "no more than ***6*** months" to "no more than ***12*** months" • Revised criteria for continuation of therapy; replaced criterion requiring "documentation of continued clinical benefit, including an evaluation with a standardized assessment of motor function ability by a neurologist with experience in treating Duchenne muscular dystrophy" with "documentation of continued clinical benefit *based on prescriber's assessment*, including an evaluation with a standardized assessment of motor function ability by a neurologist with experience in treating Duchenne muscular dystrophy" **Supporting Information** • Archived previous policy version CSPA2023D0058I

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. 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.

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