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UnitedHealthcare Community Plan

UnitedHealthcare® Community Plan
Medical Benefit Drug Policy

EXONDYS 51® (ETEPLIRSEN)

Policy Number: CSLA2019D0058F **Effective Date**: TBD

Instructions for Use

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Related Community Plan Policy
- Exondys 51® (Eteplirsen) (for Pennsylvania Only)

Commercial Policy
- Exondys 51® (Eteplirsen)

APPLICATION

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

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; and**
  - **Submission of medical records (e.g., chart notes, laboratory values) confirming that the patient has a 6-Minute Walk Time (6MWT) ≥ 300 meters while walking independently (e.g., without side-by-side assist, cane, walker, wheelchair, etc.) prior to beginning Exondys 51 therapy; 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: maximum dosing of 30 mg/kg infused once weekly; and**
  - **Exondys 51 is not used concomitantly with other exon skipping therapies for DMD (e.g., Vyondys 53); and**
  - **Initial authorization will be for no more than 8 weeks.**

- **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**
  - **Submission of medical records (e.g., chart notes, laboratory values) demonstrating that the patient continues to have a 6-Minute Walk Time (6MWT) ≥ 300 meters while walking independently (e.g., without side-by-side assist, cane, walker, wheelchair, etc.). This must be measured no earlier than 4 weeks prior to a continuation request; and**

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- **Exondys 51 dosing for DMD is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 30 mg/kg infused once weekly; 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 6 months.**

~~Exondys 51® (eteplirsen) is not medically necessary for treatment of Duchenne muscular dystrophy (DMD) due to lack of scientific evidence showing clinical benefit and efficacy.~~

~~The FDA labeled indication includes a statement that a clinical benefit has not been established and continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.~~

~~Therapies shall be deemed medically necessary in accordance with federal, state or contractual requirements for benefit coverage.~~

~~Upon review, services that are not found to be medically necessary will not be approved for coverage.~~

~~The fact that a physician or other healthcare practitioner has prescribed a treatment, or the fact that it may be the only treatment for a particular injury, sickness, or condition, does not mean that it is medically necessary.~~

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

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

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. A clinical benefit of Exondys 51 has not been established. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials. [1]

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. Exon skipping is intended to allow for production of an internally truncated dystrophin protein. [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 Coverage Determination Guidelines may apply.

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HCPCS Code	Description
J1428	Injection, eteplirsen, 10 mg

ICD-10 Diagnosis Code	Description
G71.01	Duchenne or Becker muscular dystrophy

CLINICAL EVIDENCE

The Food and Drug Administration (FDA) approved eteplirsen 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] Eteplirsen, was under priority review and granted accelerated approval. Priority review designation is given to drugs that provide significant advances in treatment, or treat disease where no adequate therapy exists. Accelerated approval allows for earlier approval of drugs that treat serious conditions, and that fill an unmet medical need based on a surrogate endpoint. On April 25th, 2016, the Peripheral and Central nervous System Drugs Advisory Committee convened. A majority of the committee found that the clinical results of the single historically-controlled study (Study 201/202) (Mendell 2013, Mendell 2016) did not provide substantial evidence that etelplirsen is effective for the treatment of DMD, and voted against approval. On September 19, 2016, the FDA approved eteplirsen based on an increase in dystrophin in skeletal muscle observed in some patients treated with eteplirsen. Section 1 (Indications and Usage) of the FDA prescribing information states that a clinical benefit of eteplirsen has not been established and continued approval for this indication is contingent upon verification of a clinical benefit in confirmatory trials. Despite approval, it is unknown whether the small increase of dystrophin at the molecular level will translate to any clinical meaningful benefit. [1,6,7]

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 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. [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. 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,

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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 ($p \leq 0.001$). Both at 24 and 48 weeks, eteplirsen did not show an advantage over placebo on the 6MWD. The 6-minute walk distance data was not included in the prescribing information, because the FDA communicated that these data did not constitue substantial evidence of efficacy. The advisory committee found that these studies did not provide substantial evidence that eteplirsen induces production of dystrophin to a level that is reasonably likely to predict clinical benefit. Finally, the advisory committee also found that the results of these historically-controlled studies did not provide substantial evidence that eteplirsen is effective for the treatment of DMD.

The FDA's approval was also based on an ongoing, unpublished , confirmatory study (Study 3 in the prescribing information, PROMOVI, NCT02255552). PROMOVI is an open-label, multi-center 48 week study that includes boys with DMD amenable to exon 51 skipping being treated with the FDA approved dosing, while boys with DMD not amenable to exon 51 will serve as conrols. As stated in the prescribing information, data from 12 of 13 enrolled patients were available at the time of publication. Dystrophin levels in muscle tissue were assessed by western blot, which levels were statistically significantly increased in the active treatment arm. A statistically significant increase in dystrophin, however, does not imply clinical benefit. [1,7,10]

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) for Exondys 51® (eteplirsen). Local Coverage Determinations (LCDs) do not exist at this time.

In general, Medicare may cover outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals.

(Accessed January 6, 2020)~~Medicare does not have a National Coverage Determination (NCD) for Exondys 51® (eteplirsen). Local Coverage Determinations (LCDs) do not exist at this time.~~

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~~(Accessed January 11, 2019)~~

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
TBD	• **Annual review. Added coverage rationale. Updated CMS statement.**

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.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The 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.

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