EXONDYS 51™ (ETEPLIRSEN)

Policy Number: 2017D0058B **Effective Date**: April 1, 2017

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Related Commercial Policy

- Specialty Medication Administration– Site Of Care Review Guidelines

INSTRUCTIONS FOR USE

This Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Drug Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Drug Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Drug Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This 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 MCG™ Care Guidelines 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.

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The enrollee-specific benefit 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. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases.

Essential Health Benefits for Individual and Small Group
For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

COVERAGE RATIONALE

Exondys 51™ (eteplirsen) may be covered for:[1]

1. The treatment of **Duchenne muscular dystrophy (DMD)** in patients who meet **all** of the following criteria:
   a. For **initial therapy**, **all** of the following:
      (1) **One** of the following:
         (a) Diagnosis of Duchenne muscular dystrophy by a neurologist with expertise in the diagnosis of DMD
         (b) Diagnosis of Duchenne muscular dystrophy by a physician in consultation with a neurologist with expertise in the diagnosis of DMD

      AND

      (2) 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

      (3) 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 prior to beginning Exondys 51 therapy.[7]

      AND

      (4) **One** of the following:
         (a) Exondys 51 is prescribed by a neurologist with expertise in the treatment of DMD
         (b) Exondys 51 is prescribed by a physician in consultation with a neurologist with expertise in the treatment of DMD

      AND

      (5) 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

      (6) Initial authorization will be for no more than 4 weeks.

   b. For **continuation therapy**, **all** of the following:
      (1) **One** of the following:
         (a) Exondys 51 is prescribed by a neurologist with expertise in the treatment of DMD
         (b) Exondys 51 is prescribed by a physician in consultation with a neurologist with expertise in the treatment of DMD

      AND

      (2) Submission of medical records (e.g., chart notes) confirming that the patient is ambulatory **without** needing an assistive device (e.g., cane, walker, wheelchair, etc.).

      AND

      (3) 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

      (4) Reauthorization will be for no more than 6 months

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

U.S. FOOD AND DRUG ADMINISTRATION

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 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 Coverage Determination Guidelines may apply.

HCPCS Code	Description

ICD-10 Diagnosis Code	Description
G71.0	Muscular dystrophy

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]

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 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]

CENTERS FOR MEDICARE AND MEDICAID SERVICES

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

In general, Medicare covers 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. See the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals at http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf.

(Accessed September 23, 2016)

REFERENCES

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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.
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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/NCT 02255552 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.

POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
4/1/2017	Revised policy. Updated coverage rationale with additional criteria. Updated clinical evidence and references. Approved by National Pharmacy & Therapeutics Committee on 2/17/2017.
2/1/2017	New policy 2017D0058A. Approved by National Pharmacy & Therapeutics Committee on 10/26/2016.