**TEMPLATE**

**Letter of Medical Necessity**

**For Medical Procedures Associated with the Administration of Exondys 51**

**Date:**

[Insert Name of Medical Director] RE: Patient Name [ ]

[Insurance Company] Policy Number [ ]

[Address] Claim Number [ ]

[City, State, Zip]

Dear [Insurance Company]:

I am writing this letter of medical necessity to provide information related to the treatment of **[insert patient name**] with EXONDYS 51tm, a drug for the treatment of Duchenne muscular dystrophy patients with specific mutations amenable to skipping exon 51. The FDA approved this drug on September 16, 2016 under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients of EXONDYS 51. The FDA’s broad label presents the opportunity to slow the progression of disease in Duchenne patients amenable to skipping exon 51.

I would like to provide the following information about the benefit of EXONDYS 51 in Duchenne patients:

**1. Duchenne pathophysiology**

Duchenne muscular dystrophy is caused by mutations in the dystrophin gene. This gene is an x-linked genetic disorder characterized by the progressive loss of skeletal muscle and degeneration, primarily in boys. It affects one out of 5000 live male births in the US 3,4. The average age at diagnosis is approximately five years 5, but delays in motor milestones (such as sitting, standing independently, climbing, and walking) occur much earlier 1. With 79 exons, the dystrophin gene is one of the largest known human genes. Its size and error-prone areas (hotspots) make it more likely to have mutations, which can be deletions or duplications of exons, small missing or extra pieces, or tiny substitutions, in genetic code. The most frequent mutation is deletion. Deletions may result in either an out of frame mutation, closing the reading frame and producing no dystrophin, or an in frame mutation, resulting in a truncated dystrophin. Exon skipping is a strategy involving splice-switching oligomers, changing an out of frame mutation (with no dystrophin production) to an in frame mutation (with truncated dystrophin production). 13% of all Duchenne patients have a genetic deletion amenable to skipping exon 51.

Dystrophin is located beneath the sarcolemma, and functions to connect the subsarcolemmal cytoskeleton to the sarcolemma7. A loss of dystrophin in muscle results in inflammation, muscle degeneration and replacement of muscle with fibroadipose (fat and fibrotic) tissue 8.

The primary symptoms of Duchenne muscular dystrophy are caused by a lack of dystrophin in the muscle. Children with Duchenne lose the ability to walk independently and most become reliant on wheelchairs for mobility by the age of 13 6. Most individuals with Duchenne experience serious respiratory, orthopedic, and cardiac complications. By the age of 18, the majority of patients require ventilation support at night 2The average life expectancy is approximately 30 years of age, with respiratory complications and cardiomyopathy being common causes of death2. Standard medical management of Duchenne requires attention to the the use of corticosteroids as well as respiratory, cardiac, orthopedic, and rehabilitative interventions aimed at the sequela that progressively worsen throughout the lifespan of Duchenne 2. The potential for corticosteroids was published in 1989 in a randomized, double blind study of over 100 patients in 1989 7. Corticosteroids slow the progression of muscle weakness and delay some of the complications of the disease, but they do not treat or correct the underlying causes of Duchenne1. **The provision of EXONDYS 51 has been shown to result in the production of truncated dystrophin, which hopes to have a positive effect on muscle degeneration7, slowing or halting the progression of this disease.**

**2. Description of EXONDYS 51**9

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. The molecular formula of eteplirsen is C364H569N177O122P30. The molecular weight is 10305.7 daltons.

**3. Mechanism of action of EXONDYS 51**9

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 but functional dystrophin protein. Studies have shown over long term follow up that eteplirsen-treated patients demonstrated a statistically significant advantage of 151m (p < 0.01) on 6MWT and experienced a lower incidence of loss of ambulation in comparison to matched HC (n = 13) amenable to exon 51 skipping. Pulmonary Function Test (PFT) results remained relatively stable in eteplirsen-treated patients.10 Eteplirsen’s clinical benefit mirrored the time required to produce consistent increases in dystrophin. Over repeated doses, Eteplirsen accesses more fiber muscles, thus allowing for more dystrophin-positive fiber production over time.

**3. Dosing Schedule of EXONDYS 51**9

Dosing for EXONDYS 51 is 30 milligrams per kilogram of body weight once weekly. Exondys 51 is supplied in single dose vials containing 100mg or 500 mg of eteplirsen (50mg/mL).

**3. Administration of EXONDYS 51**9

EXONDYS 51 is given weekly by intravenous (IV) infusion, via either peripheral or central venous access.

**4. Rationale for Treatment**

Advances in medical management have significantly improved life expectancy and quality of life. The use of corticosteroids has pushed the age at loss of ambulation to around 13 yo, demonstrating delayed decline of lower limb skeletal muscle. However, corticosteroids do not treat the underlying cause of the disease. EXONDYS 51 is intended to allow for production of an internally truncated but functional dystrophin protein. Data generated from eteplirsen studies to date support the suggestion that relatively low levels of dystrophin can be functionally significant to patients and reasonably likely to predict clinical benefit. I believe EXONDYS 51 supplied to my patient will help to preserve muscle, delaying loss of function.

**5. Summary of Patient’s History [You may want to include]:**

* Chart notes
* Genetic tests
* Copy of the patient’s insurance cards
* FDA Approval Letter
* Prescribing information
* Recent medical articles
* Letters from other specialists treating the patient such as cardiologists, pulmonologists and physical and occupational therapists
* Patient's psychological factors that are relevant to your chosen treatment
* Information to educate Medical Director or Pharmacy Director who is not familiar with the disease or treatment

**6. Patient’s prognoses**

* Summary of your professional opinion of the patient’s likely prognoses without treatment with EXONDYS 51

**7. Concluding Remarks**

Based on the clinical data available to date, it is my medical opinion that initiating treatment of **[patient name]** with EXONDYS 51 is medically appropriate and necessary and the procedures required for its administration should be a covered and reimbursed service. Below, this letter outlines **[patient name’s]** medical history, prognoses, and the rationale for treatment with EXONDYS 51 (to be completed by physician based on patient medical history and prognosis). The totality of the data available to date supports the potential benefits of treatment with EXONDYS 51. I am requesting an expedited review of this case due to the fatality of this disease.

HCP to insert information relevant to particular case (e.g., Given the patient’s history, his/her current condition, lack of treatment options for Duchenne and the emerging data of the effects of EXONDYS 51 in Duchenne patients amenable to skipping exon 51, I believe treatment of **[insert patient name]** with this product is warranted, appropriate and medically necessary. The totality of the data available to date supports the potential benefit of treatment with EXONDYS 51).

Please call my office at **[insert telephone number]** if I can provide you with any additional information. I look forward to receiving your timely response and approval of this claim.

Sincerely,

**[Insert Doctor name and**

**Participating provider number]**

**11. References**

Bushby K, Finkel F, Birnkrant DJ, et al. For the DMD Care Considerations Working Group. Diagnosis and management of Duchenne muscular dystrophy, part 1: Diagnosis, and pharmacological and psychosocial management. Lancet Neurol 2010;9:77–93.

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* 8EP Hoffman, RH Brown Jr, LM Kunkel, Dystrophin: the protein product of the Duchenne muscular dystrophy locus,Cell, 51 (1987), pp. 919–928

9Exondys 51 [package insert]. Cambridge, MA. Sarepta Therapeutics, Inc.; September 2016.

10. **J**erry R. Mendell, MD,1,2,3 Nathalie Goemans, MD, PhD,4 Linda P. Lowes, PhD,1,3

Lindsay N. Alfano, PT,1,3 Katherine Berry, PT,1,3 James Shao, MS,5

Edward M. Kaye, MD,5 and Eugenio Mercuri, MD, PhD,6 for the Eteplirsen Study Group and Telethon Foundation DMD Italian Network