**TEMPLATE**

**Letter of Medical Necessity**

**For Medical Procedures Associated with the Administration of VILTEPSO**

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 VILTEPSO®, a drug for the treatment of Duchenne muscular dystrophy patients with specific mutations amenable to skipping exon 53. The FDA approved this therapy under accelerated approval based on an increase in dystrophin in skeletal muscle observed in patients.1 The FDA’s broad label2 presents the possibility of slowing the progression of disease in Duchenne patients amenable to skipping exon 53.

I would like to provide the following information about the potential benefit of VILTEPSO in Duchenne patients:

**1. Duchenne pathophysiology**

Duchenne muscular dystrophy is caused by mutations in the dystrophin gene. The DMD 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 years5 but delays in motor milestones (such as sitting, standing independently, climbing, and walking) occur much earlier.6 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 a 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).7 An estimated 8% of all Duchenne patients have a genetic deletion amenable to skipping exon 53.10

Dystrophin is located beneath the sarcolemma, and functions to connect the subsarcolemmal cytoskeleton to the sarcolemma.7 A loss of dystrophin in muscle results in inflammation, muscle degeneration and replacement of muscle with fibroadipose (fat and fibrotic) tissue. 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 13.8 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.9 The average life expectancy is approximately 30 years of age, with respiratory complications and cardiomyopathy being common causes of death.9 Standard medical management of Duchenne requires attention to 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.9 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 Duchenne. **The provision of VILTEPSO has been shown to result in the production of truncated dystrophin10, which hopes to have a positive effect on muscle degeneration, slowing or halting the progression of this disease.**

**2. Description of VILTEPSO**

VILTEPSO (vitolarsen) is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) subclass 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 53 skipping. 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).

**3. Mechanism of action and results of clinical trials of VILTEPSO**

VILTEPSO is designed to bind to exon 53 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 53 skipping. Exon skipping is intended to allow for production of an internally truncated but functional dystrophin protein. In viltolarsen clinical trials, all participants showed significant increases in dystrophin content in their week 25 posttreatment biopsies as measured by Western blot. Participants exhibited a mean (SD) percentage of normal dystrophin levels of 5.9% (4.5%) in the high-dose cohort (80mg/kg/week). A significant difference between baseline and post treatment biopsies was observed in both treatment groups (low-dose viltolarsen cohort: change from baseline normalized to myosin heavy chain, 5.4%; P < .001; high-dose viltolarsen cohort: change from baseline normalized to myosin heavy chain, 5.3%; P = .01).10

Disease progression was measured using timed function tests and muscle strength assessments in both the 25 week study as well as the 109 long term extension study. Comparison of viltolarsen-treated participants with 65 age-matched and treatment-matched natural history controls from CINRG DNHS demonstrated evidence of clinical benefit of viltolarsen treatment. Viltolarsen-treated participants showed improvement or stabilization of function over the 25-week period whereas the CINRG DNHS external comparator group exhibited a decline in all timed function tests, except for time to climb 4 stairs. Velocity in the time to run/walk 10 m test significantly improved in viltolarsen-treated participants at weeks 13 and 25 compared with a decline in controls from CINRG DNHS (change at 25 weeks compared with baseline: viltolarsen, 0.23 m/s; control, −0.04 m/s). The 6-minute walk test showed significant improvement at week 25 in viltolarsen-treated participants, whereas results from CINRG DNHS controls declined over the same period (change at 25 weeks compared with baseline: viltolarsen, 28.9 m; control, −65.3 m). Significant improvements in time to stand from supine were observed (change at 25 weeks compared with baseline: viltolarsen, −0.19 s; control, 0.66 s). Velocity in the time to stand from supine test and time to climb 4 stairs test as well as North Star Ambulatory Assessment similarly displayed improvement or stabilization, but the differences between viltolarsen treatment and external comparator controls were not significant. Measures of muscle strength by isometric testing showed no differences between viltolarsen-treated participants and the CINRG DNHS external comparator control group.10

At the conclusion of the Phase 2 study, participants were given the opportunity to enroll in the long-term

extension (LTE) study. The primary objective of which was to evaluate the efficacy and safety of viltolarsen over a period of up to an additional 192 weeks. In an interim analysis at 109 weeks (approximately 2 years), viltolarsen-treated participants maintained time to stand from supine (TTSTAND) function whereas the CINRG DNHS group experienced functional decline (change at 109 weeks compared with baseline: viltolarsen, 0.43 s; control, 4.31 s). Improvements were significant at timepoints 73 and 109 weeks for TTSTAND (seconds) and at all timepoints for TTSTAND (velocity). Change from baseline in time to run/walk 10 meters (TTRW) likewise indicated maintenance of function through week 109 in participants treated with viltolarsen versus functional decline in the historical control group (change at 109 weeks compared with baseline: viltolarsen, -0.44 s; control, 1.29 s). Although TTCLIMB (seconds) and TTCLIMB (velocity) showed numerical improvement at all timepoints, TTCLIMB (seconds) was not significantly different from the control group, and TTCLIMB (velocity) was significantly different from the control group only at 73 weeks (viltolarsen change from baseline [CFB]: 0.05 task/s [SE 0.03], DNHS CFB: –0.05 task/s [SE 0.02]; *P* = 0.0082). This analysis at the 2-year mark suggests clinically relevant motor function was maintained and safety was similar to that observed in the previous 24-week trial, which was predominantly mild, and there have been no treatment-related serious adverse events and no discontinuations.11

**4. Dosing Schedule of VILTEPSO**2

Dosing for VILTEPSO is 80 milligrams per kilogram of body weight once weekly. VILTEPSO is supplied in single dose vials containing 250 mg/5 mL.

**5. Administration of VILTEPSO**2

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

**6. 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 years old, demonstrating delayed decline of lower limb skeletal muscle. However, corticosteroids do not treat the underlying cause of the disease. VILTEPSO is intended to allow for production of an internally truncated but functional dystrophin protein.10 Data generated from viltolarsen 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 VILTEPSO supplied to my patient will help to preserve muscle, delaying loss of function.

**7. 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

**8. Patient’s prognoses**

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

**9. Concluding Remarks**

Based on the clinical data available to date, it is my medical opinion that initiating treatment of **[patient name]** with VILTEPSO 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 VILTEPSO. 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 VILTEPSO in Duchenne patients amenable to skipping exon 53.

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]**

**References**

*FDA Approves Targeted Treatment for Rare Duchenne Muscular Dystrophy Mutation*[*https://www.fda.gov/news-events/press-announcements/fda-approves-targeted-treatment-rare-duchenne-muscular-dystrophy-mutation*](https://www.fda.gov/news-events/press-announcements/fda-approves-targeted-treatment-rare-duchenne-muscular-dystrophy-mutation)

*2 Vitolarsen (VILTEPSO) FDA label. Retrieved from:* <https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212154s002lbl.pdf>

*3 Mendell JR, Shilling C, Leslie ND, et al. Evidence Based Path to Newborn Screening for Duchenne Muscular Dystrophy. Ann Neurol 2012;71:304-313.*

*4 Mah JK, Korngut L, Dykeman J, Day L, Pringsheim T, Jette N. A systematic review and meta-analysis on the epidemiology of Duchenne and Becker muscular dystrophy. 2014;24:482-491.*

*5 Ciafaloni E, Fox DJ, Pandya S, Westfield CP, Puzhankara S, Romitti PA, et al. Delayed diagnosis in Duchenne muscular dystrophy: data from the muscular dystrophy surveillance, tracking, and research network (MD-STARnet). J Pediatr 2009;155:380-385.*

*6 Bushby K, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management Lancet Neurol 2018*

*7 Lucía Echevarría, Philippine Aupy, Aurélie Goyenvalle, Exon-skipping advances for Duchenne muscular dystrophy,*Human Molecular Genetics*, Volume 27, Issue R2, 01 August 2018, Pages R163–R172,*[*https://doi.org/10.1093/hmg/ddy171*](https://doi.org/10.1093/hmg/ddy171) *8Bello L, Gordish-Dressman H1, Morgenroth LP1, Henricson EK1, Duong T1, Hoffman EP1, Cnaan A1, McDonald CM2; CINRG Investigators. Prednisone/prednisolone and deflazacort regimens in the CINRG Duchenne Natural History Study. Neurology. 2015  
9Birnkrant DJ, Bushby K, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management Lancet Neurol 2018  
10 Clemens PR, Rao VK, Connolly AM, et al. Safety, Tolerability, and Efficacy of Viltolarsen in Boys With Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping: A Phase 2 Randomized Clinical Trial. JAMA Neurol. 2020;77(8):982–991. doi:10.1001/jamaneurol.2020.1264*

*11 Clemens, PR., et al. “Long-Term Functional Efficacy and Safety of Viltolarsen in Patients with Duchenne Muscular Dystrophy.” Journal of Neuromuscular Diseases, vol. 9, no. 4, 2022, pp. 493–501., https://doi.org/10.3233/jnd-220811.*