

TEMPLATE

Letter of Medical Necessity

For Medical Procedures Associated with the Administration of ELEVIDYS (delandistrogene moxeparvovec-rokl)

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 ELEVIDYS (delandistrogene moxeparvovec-rokl), a gene transfer therapy for the treatment of Duchenne muscular dystrophy. The FDA approved this therapy under accelerated approval based on an increase in ELEVIDYS micro-dystrophin in skeletal muscle observed in patients.¹ The FDA's label² presents the possibility of slowing the progression of disease in ambulatory Duchenne patients ages 4 to 5 years, with a confirmed mutation in the *DMD* gene who do not have a deletion including or within exon 8 and/or exon 9 in *DMD* or a pre-existing medical reason preventing treatment.

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

1. Duchenne pathophysiology

Duchenne muscular dystrophy (DMD) is an X-linked genetic disorder characterized by the progressive loss of muscle, primarily in boys. DMD is the result of variants in the dystrophin (*DMD*) gene. 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 variants, which can be deletions or duplications of entire exons, or small deletions, duplications, or substitutions within exons or introns. Gene transfer therapy is a strategy involving the development of a truncated gene product delivered by an adeno-associated viral vector designed to target skeletal and cardiac muscle restoring expression of a shortened, functional dystrophin protein⁷

Dystrophin is located beneath the sarcolemma, and functions to connect the subsarcolemmal cytoskeleton to the sarcolemma. 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 ELEVIDYS has been shown to result in the production of micro-dystrophin² which is likely to predict a positive effect on muscle degeneration, slowing or halting the progression of this disease.**

2. Description of ELEVIDYS

ELEVIDYS (delandistrogene moxeparvovec-rokl) is a recombinant gene therapy designed to deliver the gene encoding the ELEVIDYS micro-dystrophin protein. ELEVIDYS is a non-replicating, recombinant, adenoassociated virus serotype rh74 (AAVrh74) based vector containing the ELEVIDYS micro-dystrophin transgene under the control of the MHCK7 promoter. The genome within the ELEVIDYS AAVrh74 vector contains no viral genes and consequently is incapable of replication or reversion to a replicating form. The micro-dystrophin protein expressed by ELEVIDYS is a shortened version (138 kDa, compared to 427 kDa size of dystrophin expressed in normal muscle cells) that contains selected domains of dystrophin expressed in normal muscle cells.²

3. Mechanism of action and clinical trial results of ELEVIDYS²

ELEVIDYS is the recombinant gene therapy product that is comprised of a non-replicating, recombinant, adeno-associated virus (AAV) serotype rh74 (AAVrh74) capsid and a ssDNA expression cassette flanked by inverted terminal repeats (ITRs) derived from AAV2. The cassette contains: 1) an MHCK7 gene regulatory component comprising a creatine kinase 7 promoter and an α -myosin heavy chain enhancer, and 2) the DNA transgene encoding the engineered ELEVIDYS micro-dystrophin protein.

Vector/Capsid: Clinical and nonclinical studies have demonstrated AAVrh74 serotype transduction in skeletal muscle cells. Additionally, in nonclinical studies, AAVrh74 serotype transduction has been demonstrated in cardiac and diaphragm muscle cells.

Promoter: The MHCK7 promoter/enhancer drives transgene expression and has been shown in animal models to drive transgenic ELEVIDYS micro-dystrophin protein expression predominantly in skeletal muscle (including diaphragm) and cardiac muscle. In clinical studies, muscle biopsy analyses have confirmed ELEVIDYS microdystrophin expression in skeletal muscle.

Transgene: DMD is caused by a mutation in the *DMD* gene resulting in lack of functional dystrophin protein. ELEVIDYS carries a transgene encoding a micro-dystrophin protein consisting of selected domains of dystrophin expressed in normal muscle cells. ELEVIDYS micro-dystrophin has been demonstrated to localize to the sarcolemma.²

Two studies evaluated ELEVIDYS micro-dystrophin expression (expressed as change from baseline) as measured by western blot in 61 patients. Muscle biopsies were obtained at baseline prior to ELEVIDYS infusion and at Week 12 after ELEVIDYS infusion in all subjects. For subjects aged 4 through 5 years who received 1.33×10^{14} vg/kg of ELEVIDYS, the mean (SD) ELEVIDYS micro-dystrophin expression levels (change from baseline) at Week 12 following ELEVIDYS infusion were 95.7% (N=3, SD: 17.9%) in Study 1 Parts 1 and 2 and 51.7% (N=11, SD: 41.0%) in Study 2 Cohort 1.²

4. Dosing Schedule of ELEVIDYS²

ELEVIDYS is administered intravenously as a one-time infusion at a dose of 1.33×10^{14} vector genomes (VG) per kg of body weight.

ELEVIDYS is not recommended in patients with elevated anti-AAVrh74 total binding antibody titers ($\geq 1:400$).

5. Administration of ELEVIDYS²

ELEVIDYS (Delandistrogene moxeparvovec-rokl) is administered intravenously as a one-time infusion at a dose of 1.33×10^{14} vector genomes (VG) per kg of body weight.

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. ELEVIDYS is intended to allow for production of an internally truncated but functional dystrophin protein.² Data generated from ELEVIDYS 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. In a phase 1/2a nonrandomized controlled trial, 4 patients showed functional improvement of NSAA scores and reduced CK levels maintained for 1 year.¹¹ Additionally, in a phase 2, double blind, 2 part crossover study, all patients demonstrated dystrophin expression as well as stabilization of motor function up to 2 years post treatment.¹⁰ I believe ELEVIDYS supplied to my patient will help to preserve muscle, delaying loss of function.

7. Summary of Patient's History [You should also include]:

- Chart notes, including the patient's most recent weight
- Genetic tests
- Antibody titer test
- 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 prognosis

- Summary of your professional opinion of the patient's likely prognosis without treatment with ELEVIDYS. If applicable, consider including rationale for maintaining exon skipping therapy until dosing of ELEVIDYS.

9. Concluding Remarks

Based on the clinical data available to date, it is my medical opinion that initiating treatment of [patient name] with ELEVIDYS 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 ELEVIDYS. 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 ELEVIDYS in Duchenne patients amenable to treatment, expedited review if risk of patient aging out).

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

¹ U.S. Food and Drug Administration, STN BL 125781/0 approval letter, June 22nd 2023. <https://www.fda.gov/media/169715/download>

² Elevidys (Delandistrogene moxeparvovec) [package insert]. Silver Spring, MD: U.S. Food & Drug Administration. <https://www.fda.gov/media/169679/download>. Published June 22, 2023.

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 Chamberlain JR, Chamberlain JS. Progress toward Gene Therapy for Duchenne Muscular Dystrophy. *Mol Ther*. 2017;25(5):1125-1131

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 Mendell JR, Shieh PB, McDonald CM, et al. Expression of SRP-9001 dystrophin and stabilization of motor function up to 2 years post-treatment with delandistrogene moxeparvovec gene therapy in individuals with Duchenne muscular dystrophy. *Front Cell Dev Biol*. 2023;11:1167762.

¹¹Mendell JR, Sahenk Z, Lehman K, et al. Assessment of Systemic Delivery of rAAVrh74.MHCK7.micro-dystrophin in Children With Duchenne Muscular Dystrophy: A Nonrandomized Controlled Trial. *JAMA Neurol*. 2020;77(9):1122-1131.