



UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Muscular Dystrophy – Gene Therapy – Elevidys Utilization Management Medical Policy

- Elevidys® (delandistrogene moxeparvovec-rokl intravenous infusion – Sarepta)

REVIEW DATE: 07/19/2023

OVERVIEW

Elevidys, an adeno-associated virus (AAV) vector-based gene therapy, is indicated for the treatment of ambulatory pediatric patients aged 4 through 5 years with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the *DMD* gene.¹ This indication is approved under accelerated approval based on expression of Elevidys micro-dystrophin observed in patients treated with Elevidys. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Disease Overview

DMD is a rare, progressive X-linked disease resulting from mutation(s) of the *DMD* gene, also known as the *Dystrophin* gene.²⁻⁴ The incidence of DMD in the US is approximately 1 in 5,000 live male births. The *DMD* gene is the largest known human gene, totaling 2.3 megabases in size. The gene encodes for a functional dystrophin protein, which is part of a transmembrane protein complex that spans the sarcolemma of skeletal and cardiac muscle cells. This complex links the cytoskeleton to the extracellular matrix providing structural integrity to the sarcolemma and helps to transmit and absorb the shock associated with muscle contraction. Mutations in the *DMD* gene prevent the production of functional dystrophin protein or dystrophin is minimally produced. Without dystrophin, normal activity in patients with DMD causes excessive damage to muscle fiber cells. Over time, the muscle cells are replaced with fat and fibrotic tissue. Progressive muscle weakness is the primary manifestation of DMD. This leads to loss of ambulation, associated motor delays, respiratory impairment, and progressive decline in cardiac function. The first clinical symptoms of DMD are delay in motor development milestones, such as walking, which is observed around 2 years of age. Often there is a delay in diagnosis until the age of 3 to 5 years. Age is an important prognostic factor in the progression of DMD. There is no cure for DMD currently. The goal of treatment is to manage symptoms, slow disease progression, and to delay disability. Boys with DMD typically lose the ability to walk by age 12 or 13 years. In the past, mortality occurs by late adolescence or early twenties, however with advances in respiratory and cardiac management, some patients are living into the fourth decade. The most common cause of death for patients with DMD are respiratory failure, respiratory infection, cardiomyopathy, and cardiac arrhythmias. Corticosteroids are a mainstay of therapy in DMD; however, its mechanism of action in DMD is unknown. Corticosteroids ameliorate the symptoms of the disease and delay time to loss of ambulation and other sequelae. Four anti-sense oligonucleotide therapies (exon-skipping) have been approved by the FDA: Exondys 51® (eteplirsen intravenous infusion), Vyondys 53™ (golodirsen intravenous infusion), Viltespo™ (viltolarsen intravenous infusion), and Amondys 45™ (casimersen intravenous infusion). The clinical benefit of these exon-skipping therapies remains unknown since none of the confirmatory clinical studies have been completed.

Clinical Efficacy

The efficacy of Elevidys was evaluated in two studies:¹⁻⁴ a Phase II study and a Phase Ib study.¹ Both studies are unpublished and long-term follow-up is ongoing. The Phase II study (n = 41) included two parts: Part I was a 48-week randomized, double-blind, placebo-controlled study in which patients received a single-dose of Elevidys (n = 20) or placebo (n = 21); in Part II, patients treated with placebo in Part I received Elevidys. Patients in this study were stratified by age (age 4 to 5 years vs. age 6 to 7 years) at randomization. Retrospective analysis identified that 60% of patients in Part I received a dose lower than

Elevidys 1.33×10^{14} vector genomes (vg)/kg, due to variability in quantification methods.¹⁻³ In Part I, only 8 patients received the approved dose of Elevidys 1.33×10^{14} vg/kg; 12 patients received one-half to two-thirds of the approved dose. In Part II, all patients from the placebo group received the recommended dose of Elevidys 1.33×10^{14} vg/kg.

Guidelines

Elevidys is not addressed in current guidelines for DMD. The guidelines from the DMD Care Considerations Working Group (2018) notes that genetic testing for confirming DMD diagnosis is always required.⁵⁻⁷ In patients with no mutations identified, but with signs/symptoms of DMD, a muscle biopsy is clinically indicated. Glucocorticoids and physical therapy are the mainstays of treatment and should be continued even after the patient is non-ambulatory. Corticosteroids reduce the risk of scoliosis and stabilizes pulmonary function. In patients who are non-ambulatory, continuing corticosteroid treatment provides a reduction in the risk of progressive scoliosis and stabilization of pulmonary function tests. Due to this benefit, glucocorticoids should be considered in all patients with DMD.

Dosing

The recommended dose is 1.33×10^{14} vg/kg of body weight (or 10 mL/kg body weight).¹ Immune responses to the AAVrh74 vector can occur after Elevidys administration. To reduce this risk, corticosteroids should be administered starting one day prior to Elevidys infusion and continued for a minimum of 60 days after the infusion, unless earlier tapering is clinically indicated.

Safety

Elevidys is contraindicated in patients with any deletion in exon 8 and/or exon 9 in the *DMD* gene.¹ Warnings/Precautions are for acute serious liver injury, immune-mediated myositis, myocarditis, and pre-existing immunity against AAVrh74. For administration of Elevidys, the anti-AAVrh74 total antibody binding titer should be $< 1:400$.

POLICY STATEMENT

Due to the lack of clinical efficacy data, **approval is not recommended** for Elevidys.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Elevidys clinical data are limited and available data are not supportive of general approval for the following conditions:

- 1. Duchenne Muscular Dystrophy (DMD).** Approval is not recommended due to the unclear clinical benefit of Elevidys. Elevidys clinical trials had numerous study limitations.¹⁻⁴ In the Phase II study, Part I, the only double-blind, placebo-controlled part of the clinical trials, only 40% of the patients randomized to Elevidys (n = 8/20) received the intended gene therapy dose. The other clinical trial was a Phase Ib study that was limited by a single-arm, open-label design. In both these trials, the primary efficacy measure was the change in micro-dystrophin expression level from baseline to Week 12. It is unknown whether increases in micro-dystrophin expression will correlate with clinically meaningful functional improvements. Micro-dystrophin is a novel synthetic protein that is much smaller in size compared with that of the dystrophin protein. So although there was about a 40% increase (compared to control) in micro-dystrophin expression from baseline to post-Elevidys infusion, especially in the Phase II study, this did not translate to an increase in the functional scores, as assessed by the North Star Ambulatory Assessment (NSAA). There is no established baseline minimal percentage expression of micro-dystrophin required to show functional changes in DMD. In the double-blind study, only the subgroup of patients 4 through 5 years of age demonstrated an improvement in the NSAA total score at Week 48 compared with placebo. The subgroup of patients 6 through 7 years of age had a decrease in the NSAA total score compared with placebo, which is contrary to the expected result. Based on this unconvincing NSAA data, the FDA narrowed the age indication for Elevidys to 4 through 5 years, instead of the overall study population (age 4 through 7). Due to this age limitation, the micro-dystrophin primary endpoint in this FDA-approved group, could only be assessed in 3 patients. In the Phase Ib study there was an increase of 4 points in the NSAA total score from baseline to Week 52 in the cohort of patients (n = 20) that received Elevidys. However, the interpretation of data are limited in this study due to its open-label, single-arm design. EMBARK is a randomized, placebo-controlled, double-blind Phase III study with Elevidys that is ongoing. The preliminary results from this study are expected at the end of 2023.
- 2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.**

REFERENCES

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5. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. *Lancet Neurol.* 2018;17(3):251-267.
6. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. *Lancet Neurol.* 2018;17(4):347-361.
7. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 3: primary care, emergency medicine, psychological care, and transitions of care across the lifespan. *Lancet Neurol.* 2018;17(5):445-455.

HISTORY

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Type of Revision	Summary of Changes	Review Date
New Policy	--	07/19/2023