



Drug Coverage Policy

Effective Date 11/1/2024
Coverage Policy NumberIP0571
Policy Title.....Elevidys

Muscular Dystrophy – Gene Therapy – Elevidys

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

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer’s particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer’s benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer’s benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Conditions Not Covered

Elevidys is considered to be experimental, investigational, or unproven due to insufficient data establishing safety, efficacy, and improved health outcomes for any condition.

The current Elevidys efficacy information is insufficient to determine if the medication demonstrates any clinically meaningful benefits. In the absence of additional clinical trials, there is not enough information to support approval.

1. Duchenne Muscular Dystrophy (DMD). Approval is not recommended due to the unclear clinical benefit of Elevidys. Elevidys clinical trials had numerous study limitations.^{1-4,7-9} EMBARK is a randomized, placebo-controlled, double-blind Phase III confirmatory study with Elevidys. The primary endpoint of change from baseline to Week 52 in North Star Ambulatory Assessment (NSAA) total score was not significantly different for the Elevidys and placebo-treated groups. 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 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.

Overview

Elevidys, an adeno-associated virus (AAV) vector-based gene therapy, is indicated for the treatment of individuals at least 4 years of age with Duchenne muscular dystrophy (DMD).¹ Per the FDA label, it is specifically indicated in the following:

- For patients who are ambulatory and have a confirmed mutation in the *DMD* gene.
- For patients who are non-ambulatory and have a confirmed mutation in the *DMD* gene. The DMD indication in non-ambulatory patients is approved under accelerated approval based on expression of Elevidys micro-dystrophin in skeletal muscle. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).¹

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), Viltepso[™] (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 three studies:^{1-4,7-9} the EMBARK Phase III randomized, double-blind, placebo-controlled, confirmatory trial; a Phase II study; and a Phase Ib study. In EMBARK (n = 125), the primary endpoint of change from baseline to Week 52 in the North Star Ambulatory Assessment (NSAA) total score was not significantly different for the Elevidys and placebo-treated groups. The between-group difference least squares mean (LSM) was 0.65 points (95% confidence interval [CI]: -0.45, 1.74; P = not significant). 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 x 10¹⁴ 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 x 10¹⁴ 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 x 10¹⁴ 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 x 10¹⁴ vg/kg of body weight (or 10 mL/kg body weight) for patients weighing < 70 kg or 9.31 x 10¹⁵ vg total fixed dose for patients ≥ 70 kg.¹ Re-administration of Elevidys is not recommended. 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.

Coding Information

- 1) This list of codes may not be all-inclusive.
- 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J1413	Injection, delandistrogene moxeparvovec-rokl, per therapeutic dose

References

1. Elevidys® intravenous infusion [prescribing information]. Cambridge, MA: Sarepta Therapeutics, Inc.; June 2024.
2. US Food and Drug Administration. Cellular, Tissue, and Gene Therapies Advisory Committee Meeting. May 12, 2023. Available at: <https://www.fda.gov/advisory-committees/advisory-committee-calendar/cellular-tissue-and-gene-therapies-advisory-committee-may-12-2023-meeting-announcement-05122023> Accessed on May 10, 2023.
3. Sarepta Therapeutics, Inc. Sponsor Briefing Document. Cellular, Tissue, and Gene Therapies Advisory Committee Meeting. May 12, 2023. Available at: <https://www.fda.gov/advisory-committees/advisory-committee-calendar/cellular-tissue-and-gene-therapies-advisory-committee-may-12-2023-meeting-announcement-05122023> Accessed on May 10, 2023.
4. 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. DOI: 10.3389/fcell.2023.1167762.
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.
8. Zaidman C.M., Proud C.M., McDonald C.M., et al. Delandistrogene moxeparvovec gene therapy in ambulatory patients (aged >4 to <8 years) with Duchenne muscular dystrophy: 1 year interim results from SRP-9001-103 (ENDEAVOR). *Ann Neurology.* 2023;94(5):955-968.
9. Mendell JR, Muntoni F, McDonald CM, et al. Safety and efficacy of delandistrogene moxeparvovec versus placebo in Duchenne muscular dystrophy (EMBARK): Pivotal Phase 3 primary results. Presented at: The Muscular Dystrophy Association (MDA) 2024 Clinical & Scientific Conference; Orlando, USA; March 3-6, 2024.

Revision History

Type of Revision	Summary of Changes	Approval Date
New		11/28/2023
Annual Revision	<p>Policy Name. Updated from "Muscular Dystrophy – Gene Therapy – Elevidys (delandistrogene moxeparvovec-rokl intravenous infusion)" to "Muscular Dystrophy – Gene Therapy – Elevidys"</p> <p>Conditions Not Covered. Added "The current Elevidys efficacy information is insufficient to determine if the medication demonstrates any clinically meaningful benefits. In the absence of additional clinical trials, there is not enough information to support approval."</p>	11/1/2024

The policy effective date is in force until updated or retired.

"Cigna Companies" refers to operating subsidiaries of The Cigna Group. All products and services are provided exclusively by or through such operating subsidiaries, including Cigna Health and Life Insurance Company, Connecticut General Life Insurance Company, Evernorth Behavioral Health, Inc., Cigna Health Management, Inc., and HMO or service company subsidiaries of The Cigna Group. © 2024 The Cigna Group.