LOUISIANA BLUE

delandistrogene moxeparvovec-rokl (Elevidys®)

Policy # 00859
Original Effective Date: 03/11/2024
Current Effective Date: 03/10/2025

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of delandistrogene moxeparvovec-rokl (Elevidys®)‡ for the treatment of patients greater than or equal to 4 years of age with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the *DMD* gene to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of delandistrogene moxeparvovec-rokl (Elevidys) for non-FDA approved indications to be **investigational.***

Background/Overview

Elevidys is a gene therapy indicated for one-time infusion in patients greater than or equal to 4 years of age with a confirmed mutation in the *DMD* gene. The indication for approval in non-ambulatory patients is approved under accelerated approval based on expression of micro-dystrophin. Continued approval for use in non-ambulatory patients may be contingent upon verification and description of clinical benefit in a confirmatory trial. Elevidys uses an AAV viral vector to deliver a truncated form of the dystrophin gene known as micro-dystrophin to muscle cells. The gene then drives the production of micro-dystrophin in these cells which is theorized to work in place of the missing dystrophin protein. It is contraindicated in patients with any deletion in exon 8 and/or exon 9 in the *DMD* gene due to the increased risk of immune-mediated myositis in these patients. Risk of immune-mediated myositis may also be elevated in patients with mutations in exons 1-17 and 59-71 of the *DMD* gene, but these are not listed as contraindications in the product label.

DMD is a progressive, X-linked, degenerative neuromuscular disease that results in disabling muscle weakness and eventually leads to early death. It is caused by mutations in the *DMD* gene resulting in reduced or near absence of dystrophin, a protein that helps keep muscle cells intact. Boys with DMD are typically diagnosed at 3-5 years of age, and the estimated U.S. prevalence of DMD ranges from 10,000 to 15,000 males. There is no curative treatment for DMD. Current pharmacological approaches include corticosteroids and exon-skipping therapies. Corticosteroids, such as deflazacort (Emflaza™)‡ are the standard of care for treatment of DMD due to their beneficial effects for

improving motor function and pulmonary function, reducing the risk of scoliosis, delaying the loss of ambulation, and possibly delaying progression of cardiomyopathy and improving survival. Exon-skipping therapies work to increase dystrophin protein expression in patients that have skippable deletions in exons 51, 53, or 45, representing about 30% of the DMD population. Exon-skipping therapies increase dystrophin protein expression and may at best slow disease progression, but have not been proven to improve survival or functional outcomes.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Elevidys was approved in June 2023 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. In June 2024, the label was updated to include all patients greater than or equal to 4 years of age with a confirmed mutation in the *DMD* gene.

This indication for use in non-ambulatory patients 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).

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Both the accelerated as well as subsequent traditional approval of Elevidys by the FDA was in contrast to the recommendations made by FDA internal review teams, which did not recommend approval based upon their overall evaluation of the data submitted. The initial decision for accelerated approval was based on a post-hoc subgroup exploratory analysis of North Star Ambulatory Assessment (NSAA) total score in 16 individuals (of the total 41 in Study 102) ages 4 through 5 years and also considered the use of biomarker data from cohort 1 of Study 103 that included 20 ambulatory males aged 4 through 7 years. The subsequent decision for traditional approval was based on a statistically significant difference in three secondary efficacy endpoints, including time to rise from the floor, 10-meter walk/run (10-MWR), and time to ascend 4 steps even though the study failed to meet the primary endpoint of change in NSAA total score from baseline to week 52 post treatment.

The efficacy of Elevidys was evaluated in two double-blind, placebo-controlled studies (Study 1 and Study 3) and one open-label study (Study 2) in which a total of 214 male patients with a confirmed disease-causing mutation in the *DMD* gene were dosed.

Study 1 is a completed multi-center study including:

- Part 1: a 48-week, randomized, double-blind, placebo-controlled period.
- Part 2: a 48-week period that began following completion of Part 1. Patients who received placebo during Part 1 were treated with Elevidys, and patients treated with Elevidys during Part 1 received placebo.

The study population consisted of male ambulatory DMD patients (n=41) aged 4 through 7 years with either a confirmed frameshift mutation, or a premature stop codon mutation between exons 18 to 58 in the *DMD* gene.

Patients were randomized 1:1 to receive either Elevidys (n=20) or placebo (n=21) as a single intravenous infusion via a peripheral limb. Randomization was stratified by age (i.e., aged 4 to 5 years vs ages 6 to 7 years). In the Elevidys group, eight patients received 1.33×10^{14} vg/kg of Elevidys, and 12 patients received lower doses.

All subjects were on a stable dose of corticosteroids for DMD for at least 12 weeks prior to Elevidys infusion. All randomized subjects had baseline anti-AAVrh74 antibody titers <1:400 as determined by an investigational total binding antibody ELISA. One day prior to treatment with Elevidys or placebo, the subject's background dose of corticosteroid for DMD was increased to at least 1 mg/kg of a corticosteroid (prednisone equivalent) daily and was continued at this level for at least 60 days after the infusion, unless earlier tapering was clinically indicated.

The primary objectives of Study 1 were to evaluate expression of Elevidys micro-dystrophin in skeletal muscle, and to evaluate the effect of Elevidys on the North Star Ambulatory Assessment (NSAA) total score. The mean change from baseline in the percentage of Elevidys micro-dystrophin compared to control was 43.4 in part 1 and 40.7 in part 2. The change in NSAA total score was assessed from baseline to Week 48 after infusion of Elevidys or placebo. The difference between the Elevidys and placebo groups was not statistically significant (p=0.37). The least squares (LS) mean changes in NSAA total score from baseline to Week 48 was 1.7 (standard error [SE]: 0.6) points for the Elevidys group and 0.9 (SE:0.6) points for the placebo group. Exploratory subgroup analyses showed that for subjects aged 4 through 5 years, the LS mean changes (SE) in NSAA total score from baseline to Week 48 were 4.3 (0.7) points for the Elevidys group, and 1.9 (0.7) points for the placebo group, a numerical advantage for Elevidys. For subjects aged 6 through 7 years, the LS mean changes (SE) in NSAA total score from baseline to Week 48 were -0.2 (0.7) points for the Elevidys group and 0.5 (0.7) points for the placebo group, a numerical disadvantage for Elevidys.

Study 2 is an ongoing, open-label, multi-center study which includes 5 cohorts of 48 male DMD patients. Patients in cohorts 1, 2, and 3 have a confirmed frameshift mutation, splice site mutation, or premature stop codon mutation anywhere in the *DMD* gene while patients in cohort 4 included those with mutations in the *DMD* gene starting at or after exon 18. All patients in cohort 5 had mutations that partially or fully overlap with exons 1-17 in the *DMD* gene. All subjects had baseline anti-AAVrh74 antibodies titers <1:400 as determined by the investigational total binding antibody ELISA and received a single intravenous infusion of 1.33×10^{14} vg/kg Elevidys if they weighed less than 70 kg or 9.31×10^{15} vg/kg total fixed dose if they weighted 70 kg or greater.

The primary objective of the study was to evaluate the effect of Elevidys micro-dystrophin expression as measured by western blot. The mean change from baseline at Week 12 was found to be 51% (standard deviation 47) in ambulatory patients and 40.1% (standard deviation 35.9) in non-ambulatory patients.

Study 3 is a multi-center, randomized, double-blind, placebo-controlled study in which 125 ambulatory male patients aged 4 through 7 years, with a confirmed frameshift, splice site, premature stop codon, or other disease-causing mutation in the *DMD* gene starting at or after exon 18 were dosed. Patients with exon 45 (inclusive), or in-frame deletions, in-frame duplications, and variants of uncertain significance, were excluded. Patients received corticosteroids for DMD before infusion. All patients had baseline anti-AAVrh74 antibodies titers <1:400 as determined by the investigational total binding antibody ELISA and received a single intravenous infusion of 1.33×10^{14} vg/kg Elevidys.

The efficacy outcome measure of the study was to evaluate the effect of Elevidys on physical function as assessed by the NSAA total score. Key secondary outcome measures were to evaluate expression of micro-dystrophin in skeletal muscle, time to rise from floor, and time of 10-meter walk/run. Additional efficacy outcome measures included time of 100-meter walk/run, and time to ascend 4 steps. Results of micro-dystrophin measured by western blot showed a mean micro-dystrophin expression at Week 12 of 34.3% (n=17, SD: 41%) compared to placebo patients of 0% (n=14, SD: 0%). The change in NSAA total score was assessed from baseline to Week 52 after infusion of Elevidys or placebo. The difference between the Elevidys (n=63) and placebo groups (n=61) was not statistically significant (p=0.24). The least squares (LS) mean changes in NSAA total score from baseline to Week 52 was 2.57 (95% CI: 1.80, 3.34) points for the Elevidys group and 1.92 (95% CI: 1.14, 2.70) points for the placebo group, with a LS mean difference from placebo of 0.65 (95% CI: -0.45, 1.74). Changes of clinical relevance were noted in three secondary efficacy endpoints including time to rise from the floor, 10-meter walk/run, and time to ascend 4 steps.

Each of these studies listed above contained multiple major limitations including lack of duration to determine benefit or harms, lack of supported clinically significant difference in effect, and/or inadequate statistical power to detect differences in age subgroups. Both randomized, placebo-controlled studies failed to show a statistically significant different in the pre-specified primary

endpoint which was change in the NSAA total score between the treated and the placebo group. The US FDA approval was based on the post-hoc exploratory analysis of secondary outcome measures such as 10-MWR and time to rise from floor. These results cannot be interpreted at face value due to the lack of pre-specification and control of type 1 error. Such post hoc analysis following an overall nonsignificant test in the overall population can only be considered as hypothesis-generating. In addition, the observed treatment effect was not substantial and of uncertain clinical significance. The upper bound of 95 percent confidence intervals of point estimates for time to rise and 10-MWR was near the zero point (no effect). Further, the observed effect on 10-MWR times test was also inconsistent with opposing results observed in the 2 trials. The decisional memorandum released by the Director of the Center for Biologics Evaluation and Research to clarify his action of overruling the staff's recommendation for a complete response letter referenced an exploratory study indicating a moderate correlation between micro-dystrophin levels and the 10-MWR as well as the time required to climb 4 steps, as supportive evidence. However, it's important to note that micro-dystrophin expression levels were measured in only 25% of the patients enrolled in Study 301. Consequently, these findings might not accurately reflect the association between micro-dystrophin and the clinical efficacy outcomes across the full study cohort. Because of all these limitations in the current evidence, an adequately powered randomized, double-blind, placebo-controlled trial is necessary to clearly ascertain the net health outcome in DMD. Lastly, biomarker data reported in studies only provides information about expression of the transgene product in cells transduced by Elevidys rather than insight into a pharmacologic effect on a known biomarker in the pathway of the disease. This product is a novel, engineered protein that contains selected domains of the normal, wild-type dystrophin expressed in healthy muscle cells. No epidemiologic or pathophysiologic evidence is available regarding the function of Elevidys micro-dystrophin. The protein differs in important ways from both the endogenous shortened forms of dystrophin in patients with Becker muscular dystrophy, and the internally truncated dystrophins expressed through exon-skipping drugs. Thus, the clinical benefit of treatment DMD with Elevidys, including improved motor function and pulmonary function, has not been demonstrated. A confirmatory, prospective, and adequately powered trial is necessary to assess the net health outcome of Elevidys in patients with DMD. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

References

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Policy History

Original Effective Date: 03/11/2024
Current Effective Date: 03/10/2025

02/01/2024	Medical Policy Committee review
02/14/2024	Medical Policy Implementation Committee approval. New policy.
11/07/2024	Medical Policy Committee review
11/13/2024	Medical Policy Implementation Committee approval. Updated coverage statements and background information to reflect full FDA approval for ambulatory patients 4 years of age and older and accelerated approval for non-ambulatory patients.
02/06/2025	Medical Policy Committee review.
02/12/2025	Medical Policy Implementation Committee approval. Updated background information to include summaries of evidence. No change to coverage.

Next Scheduled Review Date: 02/2026

Coding

The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2024 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J1413
ICD-10 Diagnosis	G71.01

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.