Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCNEU042.0824	**NEUROMUSCULAR DRUGS** **ELEVIDYS®** (delandistrogene moxeparvovec-rokl suspension, for intravenous infusion)
Effective Date: 10/1/2024	**Review/Revised Date**: 07/24 (JCN)
Original Effective Date: 04/24	**P&T Committee Meeting Date**: 02/24, 08/24
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY:

REQUIRED MEDICAL INFORMATION:
Delandistrogene moxeparvovec-rokl is not considered medically necessary for coverage due to lack of conclusive evidence confirming clinical efficacy.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Delandistrogene moxeparvovec-rokl (Elevidys®), is a adeno-associated virus vector-based gene therapy for treatment of Duchenne muscular dystrophy (DMD). Treatment is intended to slow or stabilize progression.

FDA APPROVED INDICATIONS:

1. Ambulatory patients, at least 4 years of age, with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the dystrophin (*DMD*) gene.

2. Non-ambulatory patients, at least 4 years of age, with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the dystrophin (*DMD*) gene
    - This indication is approved under accelerated approval based on the surrogate endpoint of expression of Elevidys micro-dystrophin. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

POSITION STATEMENT:

Based on all currently available information, there is insufficient evidence from controlled clinical trials to establish a clinical benefit such as improved motor function; therefore, coverage of this therapy is not considered medically necessary.

There is evidence that delandistrogene moxeparvovec increased expression of Elevidys micro-dystrophin in skeletal muscle (surrogate endpoint) in ambulatory males 4-7 years with DMD[11,13]. There is some debate whether the expression of Elevidys micro-dystrophin in muscles (surrogate endpoint used for accelerated approval) is predictive of clinical benefit[4-6]. The primary clinical outcome in the placebo controlled study 102, assessed by the North Star Ambulatory Assessment (NSAA), was found not to be statistically significant. An exploratory subgroup analysis shows a numerical advantage in the NSAA score in those aged 4-5 years, Elevidys = 4.3 (0.7) points [N=8] and placebo = 1.9 (0.7) points [N=8][13]. Elevidys was first approved under accelerated approval for ambulatory males aged 4 to 5 years based on the surrogate endpoint of expression of truncated dystrophin (Elevidys micro-dystrophin) in skeletal muscle.

FDA expanded approval was based on the unpublished EMBARK trial and the open-label, single arm trial, Study 103.[18] The primary evidence of effectiveness came from the EMBARK trial, a multi-center, randomized, double-blind, placebo-controlled study in ambulatory males aged 4 to 7 years. This study was intended to be the confirmatory trial for Elevidys' accelerated approval. The study did not show a statistically significant difference in its primary endpoint, mean change is NSAA total score from baseline at Week 52. Data from Study 103, an open-label, single arm trial, was used to assess efficacy in non-ambulatory and older individuals with

DMD[18]. Elevidys has not yet been studied in a randomized trial in individuals 8 years of age or older or in non-ambulatory individuals of any age.

Background

Duchenne muscular dystrophy is a recessive X-linked genetic muscle disorder. It is a type of muscular dystrophy that affects almost exclusively males, with symptom onset usually between ages two and three with diagnosis usually by the age of five. DMD is characterized by progressive muscle weakness and atrophy which leads to respiratory failure or cardiomyopathy. Lower extremities are affected first and the ability to walk is often lost by the age of 12 or 13. There is a large heterogeneity in the disease and a standardized clinical course is not predictable. Improved respiratory and cardiac care have increased life expectancy into the fourth decade[7,10].

DMD results from mutation in the *DMD* (also known as dystrophin) gene leading to deficiency in the protein dystrophin. Dystrophin is located primarily in the skeletal and cardiac muscles. It helps strengthen muscle fibers and protect them from injury during contraction. Lack of functional dystrophin protein leads to chronic inflammation, atrophy, fibrosis, and fatty infiltration in muscles. The *DMD* (dystrophin) gene is one of the largest known human genes. DMD has a prevalence of approximately seven cases per 100,000 males worldwide. About 400-600 boys are born per year in the USA with DMD[7,10,16].

NSAA is a 17-item rating scale used to measure functional motor abilities in ambulatory children with DMD. It is used to monitor progression of the disease and treatment effects. A score of 0,1 or 2 is given in each of the 17 items. Scores range from 0-34 with higher scores indicate better performance. Highest possible score varies with age. Improvement on the NSAA can occur with standard of care alone in patients aged about four to six years. Peak scores are typically reached at six to seven years of age[4].

There is no curative treatment for DMD. Current treatment includes supportive care and medications such as corticosteroids and exon-skipping therapies.

Corticosteroids, including prednisone and deflazacort (Emflaza®) are a main stay of treatment for patients with DMD. The exact mechanism is unknown, but it is likely due to anti-inflammatory and immunomodulatory effects. Corticosteroids have been shown to slow the decline in muscle strength and function in patients with DMD[9].

Exon-skipping therapies (antisense oligonucleotides [ASOs]) target dystrophin pre-messenger ribonucleic acid (mRNA) and induce skipping of mutated exons of the

DMD gene that disrupt downstream protein synthesis and lead to nonfunctional or absent dystrophin. Skipping mutated exons results in restoration of small amount of dystrophin that may be beneficial in slowing progression of the disease, though clinical correlation has yet to be established. All four antisense oligonucleotides available were approved under accelerate approval based on a surrogate marker, dystrophin production in skeletal muscle. Confirmatory trials are still pending. The manufacturer of viltolarsen (Viltepso) announced in May 2024 that the confirmatory trial, RACERS53 Study failed to meet its primary endpoint.

American Academy of Neurology (AAN) Practice Guidelines for DMD include the following:

- Practice guideline update summary: Corticosteroid treatment of Duchenne muscular dystrophy 2016 – reaffirmed 2022
- Diagnosis and Management of DMD, Part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and GI and nutritional management - 2018
- Diagnosis and Management of DMD, Part 2: respiratory, cardiac, one health, and orthopedic management - 2018
- Diagnosis and Management of DMD, Part 3: primary care, emergency management, psychosocial care, and transitions of care across the lifespan - 2018

Guidelines address corticosteroid treatment but do not include exon skipping or gene therapy.

AAN makes the following recommendations regarding corticosteroids[9]:

- prednisone should be offered for improving strength (Level B) and pulmonary function (Level B)
- prednisone may be offered for improving timed motor function (Level C), reducing the need for scoliosis surgery (Level C), and delaying cardiomyopathy onset by 18 years of age (Level C)
- deflazacort may be offered for improving strength and timed motor function and delaying age at loss of ambulation by 1.4–2.5 years (Level C)
- deflazacort may be offered for improving pulmonary function, reducing the need for scoliosis surgery, delaying cardiomyopathy onset, and increasing survival at 5–15 years of follow-up (Level C for each)
- deflazacort and prednisone may be equivalent in improving motor function (Level C)

B = Probably effective (or probably useful/predictive) for the given condition in the specified population
C = Possibly effective (or possibly useful/predictive) for the given condition in the specified population

Micro-dystrophin as a surrogate endpoint and first FDA accelerated approval[4,5,6]:

- Elevidys micro-dystrophin is a novel, engineered protein designed to function like natural dystrophin. It contains selected portions of the normal, wild type dystrophin. The pharmacologic effect in humans is unclear. There is some debate whether the expression of micro-dystrophin in muscles is predictive of clinical benefit.
- Members of the FDA Review Committee did not consider that the available data supports the use of micro-dystrophin expression as a surrogate endpoint "reasonably likely to predict clinical benefit." They stated, "although Elevidys micro-dystrophin may have a structural effect in muscle cells, its physiological meaningfulness remains unclear.[5]"
- The director of the Center for Biologics Evaluation and Research at the FDA; however, did find expression of micro-dystrophin reasonably likely to predict clinical benefit in the specific population of four to five year olds. This was based on the exploratory subgroup analysis efficacy data in 4- to 5-year-olds (4.3 mean point increase compared to the 1.9 mean point increase which correlated with increased levels of micro-dystrophin protein expression).
- The Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) met on May 12, 2023, and voted eight to six in favor of accelerated approval. Some of the members who voted in favor of approval noted compelling data from the four year follow up of study 101 and had reservations regarding the clinical study evidence as well as the use of micro-dystrophin as a surrogate endpoint "reasonably likely to predict clinical benefit.
- The Review Committee found the available data was not adequate to meet the threshold for accelerated approval and did not recommend approval of delandistrogene moxeparvovec. The decision to not approve accelerated approval of delandistrogene moxeparvovec (Elevidys) was overridden by the director of the Center for Biologics Evaluation and Research at the FDA.

On June 22, 2023, the FDA approved delandistrogene moxeparvovec (Elevidys) for the treatment of ambulatory pediatric patients aged four through five years with Duchenne muscular dystrophy (DMD). This indication was approved under accelerated approval based on the surrogate endpoint of expression of truncated dystrophin (Elevidys micro-dystrophin) in skeletal muscle.

FDA traditional approval and expanded approval

Two different FDA reviews concluded that the available data does not verify the clinical benefit of Elevidys and recommended against approval of a label expansion.[19,20] The FDA clinical, clinical pharmacology, and statistical review of the supplemental Biologics License Application (sBLA) for Elevidys concluded that the EMBARK study along with Study 103 do not provide evidence to verify and confirm the benefit of Elevidys in ambulatory four to five year olds or for the expanded

indication to other ages and non-ambulatory patients with DMD.[20] The review highlighted that the EMBARK study failed to meet its primary endpoint and analyses of secondary endpoints was not prespecified and are therefore considered exploratory only. With respect to Study 103, it was an open-label study with exploratory efficacy endpoints. The expression of Elevidys micro-dystrophin in muscle biopsy tissue was the primary endpoint. The review noted the uncertainty of the clinical meaningfulness of this change in micro-dystrophin and its use as a surrogate endpoint.[20] Analysis of the secondary endpoints neither confirms nor disproves a benefit. In a memorandum, the Director of the Office of Clinical Evaluation (Cell and Gene Therapies) within the Super Office of Therapeutics Products (OTP) of the Center for Biologics Evaluation and Research (CBER) at the FDA, in concurrence with the Super Office Director, OTP, CBER, stated that she agrees the data provided does not support a label expansion. Regarding, the EMBARK study for ambulatory males, she notes the exploratory nature of the secondary endpoints and the lack of control of a Type 1 error.[19]

The Director of the Center for Biologics Evaluation and Research (CBER) at the FDA, Peter Marks, determined that the there is evidence that verifies the clinical benefit of Elevidys for the treatment of DMD in ambulatory patients four years and older supporting traditional approval and sufficient evidence for the accelerated approval in non-ambulatory patients four years and older based on expression of Elevidys micro-dystrophin.[18] In his memorandum he wrote the following with respect to the EMBARK study:

> "…I find that the observations regarding the secondary endpoints and exploratory endpoints are compelling and, combined with other data provided in the efficacy supplement and the original BLA, meet the substantial evidence of effectiveness… to support traditional approval in the ambulatory population. These endpoints include improvements in time to rise from the floor, 10MWR, Ascend4, and CK levels."

The memorandum indicates data to support accelerated approval in non-ambulatory individuals includes the increase in micro-dystrophin following Elevidys and Upper Limb assessment data from 6 non-ambulatory patients in Study 103. Accelerated approval for use in non-ambulatory individuals is based on the expression of Elevidys micro-dystrophin.[18]

Clinical Trials:

- FDA BLA submission includes data from three interventional clinical trials of delandistrogene moxeparvovec
  - Study 101 – phase 1, open label, single arm, N=4, safety was primary endpoint
  - Study 102 – phase 2, R, DB, PC
  - Study 103 – phase 1, open label, single arm, ongoing

Table 1: Summary of clinical trial NCT03769116 and NCT04626674

	Study 102 - Phase 2 (NCT03769116)	Study 103 - Phase 1 (NCT04626674)
Study Design	Part 1: R(1:1), DB, PC Part 2: Cross-over with blinding from part 1 Part 3: ongoing open-label follow up	Part 1: open label, single arm, 5 cohorts - focus on cohort 1 only Part 2: 5 year follow up
Study Duration	Part 1: 48 weeks Part 2: 48 weeks	Part 1: 12 weeks
Patient Population	N= 41 Ambulatory (walk independently) males aged 4 -7 with either a confirmed frameshift mutation or a premature stop codon mutation between exons 18 and 58 in the *DMD* gene.	Cohort 1 N=20 Ambulatory males aged 4–7 with a confirmed frameshift mutation, canonical splice site mutation, or premature stop codon mutation in the *DMD* gene (exons 18-79).
Key Inclusion criteria	• On stable dose of corticosteroids for ≥ 12 weeks prior to infusion • Baseline anti-AAVrh74 antibody titers <1:400	• On stable dose of corticosteroids for ≥ 12 weeks prior to infusion • Baseline anti-AAVrh74 antibody titers <1:400
Key exclusion criteria	• Exposure to an investigational or commercial gene therapy product • Exposure to another investigational drug or exon-skipping medication within 6 months of screening	Exposure to gene therapy, investigational medication, or any treatment designed to increase dystrophin expression within protocol-specified time limits.
Intervention	• Peripheral IV infusion of either placebo or Elevidys • Part 1 dose: 1.33×10^{14} vg/kg (N = 8; intended dose), 12 patients received lower doses • Part 2: all received intended dose	Single peripheral IV infusion of 1.33×10^{14} vg/kg
Primary Endpoints	• Change from baseline in quantity of micro-dystrophin expression as measured by western blot at Week 12. • Change from baseline NSAA total score at Week 48.	Change from baseline in quantity of micro-dystrophin expression as measured by western blot at Week 12.

Results			
Baseline Characteristics	• Mean age: 6.3 years (range, 4.34–7.98 years) • Mean weight: 22.4 kg (range, 15.0–34.5 kg) • Mean time to rise from floor: 4.3 seconds (range, 2.7–10.4 seconds) • Mean NSAA total score: 21.2 points (range, 13–29 points) • Unbalanced scores for NSAA ○ Elevidys group 19.8 (3.3 SD) vs placebo 22.6 (3.3 SD) • Stratified by age not functional status • For sub-group analysis ages 4-5 (N=16) → well matched at baseline • Mean NSAA score: Elevidys group 20.1 (1.9 SD) vs placebo 20.4 (2.7 SD) • For sub-group analysis ages 6-7 (N=25) • Mean NSAA score: Elevidys group 19.6 (4.1 SD) vs placebo 24 (2.9 SD)		• Mean age: 5.81 years (range, 4.38–7.94 years) • Mean weight: 21.2 kg (range, 15.2–33.1 kg) • Mean NSAA total score: 22.1 points (range, 18–26 points) • Mean time to rise from floor: 4.2 seconds (range, 2.4–8.2 seconds)
Primary Endpoint			
Western blot (% of Elevidys micro-dystrophin compared to control)[1]	Part 1 (N = 6)	Part 2 (N = 21)	Cohort 1 (N = 20)
Mean change from baseline (SD)	43.4% (48.6)	40.7% (32.3)	54.2 (42.6)
Median change from baseline (min, max)	24.3% (1.6, 116.3)	40.8% (0.0, 92.0)	50.6 (4.8, 153.9)
NSAA Total Score			
Overall	Least-squares (LS) mean treatment difference between Elevidys, and placebo was not		N/A

	statistically significant: Difference = 0.8 (95% CI: −1.0, 2.7; P = 0.37)	
Exploratory sub-group analysis for 4-5 years [LS mean change (SE)]	Elevidys = 4.3 (0.7) points [N=8] Placebo = 1.9 (0.7) points [N=8] *Trend correlating increased micro-dystrophin and improvement in NSAA score	
Exploratory sub-group analysis for 6-7 years [LS mean change (SE)]	Elevidys = -0.2 (0.7) points [N=11] Placebo = 0.5 (0.7) points [N=13]	
Safety From all trials	No deaths, 2 cases immune medicated myositis (1 life threatening), other serious adverse events include rhabdomyolysis, increased transaminases, liver injury, myocarditis, and troponin elevations. Most common reported side effects were nausea, vomiting, acute liver injury, pyrexia, and thrombocytopenia.	

[1]Information from Elevidys package insert.

- FDA sBLA submission includes data from the confirmatory trial EMBARK and Study 103, a phase 1, open label, single arm uncontrolled trial.
- Study 103 was used to assess efficacy in non-ambulatory and older patients.
    - Exploratory efficacy endpoints: NSAA, Performance of Upper Limb (PUL) Version 2.0 [for non-ambulatory], 100-MWR time, Time to Rise, Time to Ascend 4 Steps, 10-MWR time
        - Non-ambulatory (N=8), Cohort 3 (mutations between exons 18-79, N=6) & cohort 5b (mutation in exons 1 to 17, N=2)
        - Ambulatory older patients aged 8-17 years (N=7), Cohort 2
    - Cohort 2 showed a mean decline in all efficacy measures; however, cannot determine if gene therapy did not have an effect or if decline would have been greater with just standard of care as there was no control group.
    - Non-ambulatory patients in cohort 3 showed a mean decline of 3.8 points in the PUL at Week 104. The Center Director noted in his memorandum that in a natural history study of 54 non-ambulatory patients the decline was 6.3 points.[18]
    - A mean increase in expression of micro-dystrophin (primary endpoint) was observed in all five cohorts; $p<0.05$
- EMBARK – ongoing Phase 3 confirmatory trial, unpublished at time of FDA-approval

- EMBARK is a phase 3, randomized, two-part crossover, double-blind, placebo-controlled study, N=125
- Patient Population:
  - Included: Ambulatory, aged 4 through 7 years, confirmed frameshift, splice site, premature stop codon, or other disease-causing mutation in the *DMD* gene starting at or after exon 18, Time to Rise < 5 seconds, NSAA score >16 and <29, had to be on stable corticosteroid dose
  - Excluded: patients with exon 45 (inclusive), or in-frame deletions, in-frame duplications, and variants of uncertain significance, Left ventricular ejection fraction <40%, clinical signs and/or symptoms of cardiomyopathy
- Baseline Characteristics: mean age of 6 years, mean weight was 22 kg
- Results
  - Primary outcome, change from baseline in NSAA score at 52 weeks, was not statistically significant (mean difference of 0.65 points, p = 0.2441)
  - Key secondary outcomes: Difference in Time to Rise was -0.64 (-1.06, -0.23) seconds, 10-MWR was -0.42 (-0.71, -0.13) seconds, Time to Ascend 4 Steps was -0.36 (-0.71, -0.01) seconds, and in 100-MWR, was -3.29 (-8.28, 1.70) seconds

Safety

- Contraindications to delandistrogene moxeparvovec treatment include patients with any deletion in exon 8 and/or exon 9 in the *DMD* gene due to risk of immune-mediated myositis.
- Warnings and precautions include immune-mediated myositis (possible risk, with deletions in the *DMD* gene in exons 1 to 17 and /or exons 59 to 71), acute serious liver injury, myocarditis and troponin-I elevations, pre-existing immunity against AAVrh74 (baseline testing is required), infusion related reactions
- Adverse reactions with an incidence of at least 5% include vomiting and nausea, liver function test increase, pyrexia, and thrombocytopenia.
- Individuals who receive delandistrogene moxeparvovec likely cannot receive future adeno virus-based treatment due to possible immunologic cross-reactivity with other AAV subtypes.

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