Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCOTH055.1025	**MISCELLANEOUS PRODUCTS** **THERAPIES FOR DUCHENNE MUSCULAR DYSTROPHY** **Duvyzat®** (givinostat hydrochloride oral suspension)
Effective Date: 1/1/2026	**Review/Revised Date**: 10/25 (JEF)
Original Effective Date: 01/25	**P&T Committee Meeting Date**: 10/24, 10/25
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
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

REQUIRED MEDICAL INFORMATION:
For initiation of therapy (new starts), all the following must be met:

1. Confirmed diagnosis of Duchenne muscular dystrophy by genetic testing (prescriber must provide genetic test to confirm diagnosis)
2. The member is ambulatory, defined as walking without assistance
3. Documentation the member has been on a corticosteroid for at least six months, and will continue to receive a corticosteroid while on givinostat, unless contraindicated or intolerant
4. Documentation of baseline motor function prior to starting therapy with at least one appropriate standardized tool such as 4-stair climb (4SC), six-minute walk test (6MWT), North Star Ambulatory Assessment (NSAA), time to rise from the floor. Please note that this will be utilized for reauthorization.

For members established on therapy, all the following must be met:

1. Confirmed diagnosis of Duchenne muscular dystrophy by genetic testing
2. Documentation that a corticosteroid is being used concurrently with givinostat unless intolerant or contraindicated

3. Documentation of benefit of therapy as evidence by stabilization or improvement in motor function test scores performed at baseline or lack of decline compared to the natural disease progression
4. Member is ambulatory, defined as walking without assistance

Note: Medications obtained as samples, coupons, or any other method of obtaining medications outside of an established health plan benefit are NOT considered established on therapy.

EXCLUSION CRITERIA:
Use in combination with exon skipping therapies (such as Exondys 51®, Vyondys 53®, Amondys 45®, Viltepso®) and in those who have previously received gene therapy, such as Elevidys® (delandistrogene moxeparvovec)

AGE RESTRICTIONS:
May be approved for patients aged six years and older

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with a provider that specializes in the treatment of Duchenne muscular dystrophy (DMD) and/or neuromuscular disorders

COVERAGE DURATION:
Initial authorization and reauthorization will be approved for one year

QUANTITY LIMIT:
420 mL per 30 days

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.

PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCOTH055	MISCELLANEOUS PRODUCTS THERAPIES FOR DUCHENNE MUSCULAR DYSTROPHY **Duvyzat®** (givinostat hydrochloride oral suspension)

INTRODUCTION:
Givinostat hydrochloride (Duvyzat) is a histone deacetylase inhibitor. The precise mechanism of action in the treatment of Duchenne muscular dystrophy is unknown. Givinostat is the first nonsteroidal drug approved for all genetic variants of DMD. It was studied in addition to background standard of care corticosteroids in ambulatory patients not on exon-skipping therapies.

FDA APPROVED INDICATIONS:
Duchenne muscular dystrophy (DMD) in patients six years of age and older

POSITION STATEMENT:
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.[6,7]

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.[6,7,10]

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.[14]
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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 accelerated 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, givinostat or gene therapy.

AAN makes the following recommendations regarding corticosteroids[14]:

- 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)

The Institute for Clinical and Economic Review (ICER) completed a report on therapies for DMD in 2019 which included deflazacort eteplirsen, and golodirsen[15]. They had the following conclusions for deflazacort:

- Moderate certainty of comparable or better net health benefits compared with prednisone (C+)
- For deflazacort, discounts of at least 73% from its list price would be needed to achieve commonly cited thresholds for cost-effectiveness
- There are very few head-to-head trials of deflazacort and prednisone. The majority of the long-term data comparing the two drugs are from observational studies that may be subject to selection bias and lack consistent dosing and outcomes measures.

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

The review had the following conclusion for eteplirsen and golodirsen:

- *Data on the exon-skipping drugs is extremely limited and randomized trial benefits are limited to the surrogate outcome of dystrophin levels. The small increases in dystrophin levels seen in the RCTs are of uncertain clinical significance. Observational studies comparing outcomes with historical controls have suggested potential functional benefits with eteplirsen, but these data may be confounded and effort dependent. Based on the current evidence, there are no particularly concerning safety issues with either drug but given the small numbers of patients and limited follow-up, harms could be missed. We considered the data for eteplirsen and golodirsen to be insufficient ("I")*
- *No price can be suggested as a fair value-based price for eteplirsen or golodirsen because no persuasive evidence yet exists to demonstrate the clinical effectiveness of either drug*

The National Institute for Health and Care Excellence (NICE) draft guidance on the corticosteroid vamorolone (Agamree) concluded the following[16]:

- Vamorolone is not recommended, within its marketing authorization, for treating Duchenne muscular dystrophy (DMD) in people four years and over
- Vamorolone is an effective treatment for DMD, but its relative effectiveness compared with other corticosteroids was highly uncertain… [and] there was not enough evidence to conclude that vamorolone is a cost-effective treatment option.

Givinostat (Duvyzat) FDA approval was based on an 18-month randomized, double-blind placebo controlled phase 3 trial, EPIDYS, of 179 ambulant boys between six

and 17 years of age with DMD[4]. Givinostat was studied in addition to standard-of-care corticosteroids. Primary endpoint was the four-stair climb (4SC) assessment.
Key inclusion criteria:

- Ambulant males aged ≥6 years with genetically confirmed DMD
  - able to complete two 4SC with a mean of ≤8 seconds (≤1-second variance)
  - time to rise from floor between ≥3 and <10 seconds
- Has been on a stable corticosteroid dose for ≥6 months and will continue over the duration of the study

Key exclusion criteria:

- Exposure to any dystrophin restoration product (e.g., Ataluren, Exon-skipping) within six months prior to the start of study treatment or exposure to another investigational drug within 3 months prior to the start of study treatment

Results:

- Mean change from baseline in 4SC at 72 weeks was -1.25 seconds for givinostat vs -3.03 seconds for placebo; treatment difference −1.78 seconds (95% CI−3.46 to −0.11) p = 0.07.
- Key secondary outcomes such as change in NSSA score and 6-min walk test favored givinostat but were not statistically significant compared to placebo

Limitations:

- Motor function assessment tests can be dependent on motivation and method of administration. Details on the administration of the 4-stair climb test (4SC) is not published. Protocol document states tests were performed in a standardized manner as outlined in specific site manuals. Handrails could be used but information whether an individual had to perform the test the same way each assessment is not provided[12]. Method of timing (e.g., manual stopwatch or automated), is also not provided. More measurement uncertainty with manual timing.[13]
- A consensus of the minimum clinically important difference (MCID) in the 4SC is not established. One publication, with potential conflicts of interest, reports 0.035 task/s (1/4SC speed)[9] while another publication reports 2.1 seconds[11]. The first MCID relies on the baseline function. 1.78 s meets MCID of the first but not the other reported MCID.

Givinostat was reviewed by the Oregon Health Authority with the following conclusions[8]:

- Insufficient evidence to evaluate impact of givinostat on motor function outcomes in patients with DMD

- Evidence is limited by risk for performance selection and attrition bias, imprecision, and evaluation in people who are likely to have gradual disease progression

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