Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCEND047.0624	**ENDOCRINE & METABOLIC DRUGS** **CORTICOSTEROIDS FOR DUCHENNE MUSCULAR DYSTROPHY** (deflazacort tablet and suspension, vamorolone oral suspension)
Effective Date: 8/1/2024	**Review/Revised Date**: 06/17, 07/17, 10/17, 03/18, 02/19, 09/19, 02/20, 03/21, 03/22, 03/23, 03/24, 06/24 (JCN)
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Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions 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 not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
Initial authorization:

1. Confirmed diagnosis of Duchenne muscular dystrophy by genetic testing (prescriber must provide genetic test to confirm diagnosis)
2. Documentation of one of the following:
    a. The patient has tried prednisone for at least six months and has experienced one of the following clinically significant adverse events: cushingoid appearance, central (truncal obesity), weight gain of at least 10% body weight over a 6-month period or diabetes and/or hypertension that is difficult to manage according to the prescribing physician
    OR
    b. The patient has tried prednisone and has experienced psychiatric/behavioral issues (such as abnormal behavior, aggression, or irritability)
        i. The psychiatric/behavioral issues persisted beyond the first six weeks of treatment with prednisone
    AND

ii. A change in timing of prednisone administration (such as changing from morning to evening has been attempted but was unsuccessful in resolving issues

3. For Agamree: Documentation of inadequate response (after at least three months of therapy), clinically significant adverse events (such as cataracts, growth delay, reduced bone density or bone fractures), or contraindication to deflazacort
4. The dose requested is within FDA labeled dosing based on the patient's weight (patient's weight must be provided) AND dose is given in most cost effective manner (such as rounding to appropriate tablet strength or use of suspension)

Re-authorization:

1. Documentation of clinical benefit from therapy, such as improvement or stabilization of muscle strength or pulmonary function
2. The dose requested is within FDA labeled dosing based on the patient's weight (updated weight must be provided) AND dose is given in most cost effective manner (such as rounding to appropriate tablet strength or use of suspension)

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS:
Two years and up

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:
Deflazacort (Emflaza):

- 6 mg tablet: two tablets per day
- 18 mg tablet: one tablet per day

Vamorolone (Agamree): 7.5 mL (300 mg) per day

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.

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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:

Deflazacort tablet and suspension (Emflaza®) and vamorolone (Agamree®) are corticosteroids indicated in the treatment of Duchenne muscular dystrophy (DMD) in patients two years of age and older. Deflazacort is a corticosteroid prodrug, an oxazoline derivative of prednisolone. Vamorolone binds to the same target receptors as the corticosteroid class (glucocorticoid receptor, mineralocorticoid receptor), but has a different chemical structure as it lacks a 11β-hydroxyl/carbonyl moiety on the steroidal C ring. Additionally, it is an antagonist of the mineralocorticoid receptor whereas most corticosteroids are agonists. Pharmacologic activity appears to be consistent with that of other corticosteroids. [9,11]

FDA APPROVED INDICATIONS:

Duchenne muscular dystrophy (DMD) in patients two 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]

The Institute for Clinical and Economic Review (ICER) completed a report on therapies for DMD in 2019 which included deflazacort. They had the following conclusions for deflazacort[5]:

- 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.

The National Institute for Health and Care Excellence (NICE) draft guidance on vamorolone for treating Duchenne muscular dystrophy concluded the following[15]:

- Vamorolone is not recommended, within its marketing authorization, for treating Duchenne muscular dystrophy (DMD) in people 4 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.

Deflazacort (Emflaza®) was Food and Drug Administration (FDA) approved based on a phase III study that showed an improvement in strength for boys aged 5-15 with Becker or Duchenne muscular dystrophy, compared to placebo at 12 weeks, with sustained improvement at 52 weeks.

- An improvement was shown with deflazacort and prednisone compared to placebo in time from supine to stand, time to climb four stairs, and time to run or walk 30 feet. No statistically significant difference was shown between deflazacort and prednisone in these measures.
- There was less weight gain in patients treated with deflazacort. The mean change in body mass index (BMI) from baseline to week 52 was 2.29 with deflazacort vs 3.6 with prednisone.
- More patients treated with deflazacort developed cataracts, compared to patients treated with placebo.

- Post-HOC analysis suggests greater preservation of 6MWD and 4-stair climb with deflazacort versus prednisone/prednisolone. Mean changes in 6MWD were -39.0 m (deflazacort; 95% confidence limit [CL], -68.85, -9.17) and -70.6 m (prednisone/prednisolone; 95% CL, -97.16, -44.02). Mean changes in 4-stair climb were 3.79 s (deflazacort; 95% CL, 1.54, 6.03) and 6.67 s (prednisone/prednisolone; 95% CL, 4.69, 8.64). However, these are post HOC analysis and a head-to-head comparison has not been conducted.

There is evidence based on one small phase 3 trial that vamorolone improves timed motor function tests, specifically time to stand velocity (TTSTAND) and 6-minute walk test (6MWT) at 24 weeks compared to placebo in patients four to seven years of age with Duchenne muscular dystrophy. There is currently no direct efficacy comparison to prednisone or deflazacort**.** Vamorolone may have lower risk of certain adverse events such as bone turnover and fracture risk compared to prednisone.

The *VISION DMD*[9] trial was a 24 week, randomized, double blind, placebo and prednisone control trial in ambulatory corticosteroid naïve boys aged ≥ 4 to < 7 years of age (N=121) with genetically confirmed DMD who could complete the Time to Stand Test without assistance in less than 10 seconds. Secondary endpoints comparing vamorolone to prednisone were not tested.

- Intervention: Random assignment 1:1:1:1 to placebo, prednisone (0.75 mg/kg per day), vamorolone (2 mg/kg per day), and vamorolone (6 mg/kg per day)
- Primary endpoint: Efficacy – change in time to stand from supine (TTSTAND) velocity from baseline for vamorolone 6 mg/kg versus placebo
    - TTSTAND velocity is a conversion of TTSTAND. Calculated as 1/TTSTAND, expressed as rises/second.
- Secondary efficacy endpoints. Change from baseline in all the following (in order of prespecified hierarchical testing):
    - Time to stand (TTSTAND) velocity for vamorolone 2 mg/kg vs placebo
    - Six-minute walk test (6MWT) vamorolone 6 mg/kg vs placebo
    - 6MWT for vamorolone 2 mg/kg vs placebo
    - Time to walk/run (TTRW) velocity for vamorolone 6 mg/kg vs placebo
    - TTRW velocity for vamorolone 2 mg/kg vs placebo
    - 6MWT for vamorolone 6 mg/kg vs prednisone (not tested)
    - 6MWT for vamorolone 2 mg/kg vs prednisone (not tested)
- Efficacy:

Table 1. Change from baseline to week 24 in TTSTAND velocity, TTRW and 6MWT compared to placebo

Parameter	Placebo n = 28	Vamorolone 2 mg/kg n = 30	Vamorolone 6 mg/kg n = 28
TTSTAND velocity (rises/second)			
Baseline	0.200	0.184	0.186
Mean change from baseline	-0.012	0.033	0.048
Difference from placebo (95% CI)	N/A	0.045 (0.008, 0.082)	0.060 (0.023, 0.098)
p-value	N/A	0.017	0.002
6MWT (meters)			
Baseline	355	316	313
Mean change from baseline	-14	27	29
Difference from placebo (95% CI)	N/A	40 (13, 68)	42 (16, 69)
p-value	N/A	0.004	0.002
TTRW velocity (meters per second)			
Baseline	1.735	1.563	1.600
Mean change from baseline	0.014	0.141	0.258
Difference from placebo (95% CI)	N/A	**0.127 (-0.026, 0.281)**	0.244 (0.093, 0.395)
p-value	N/A	0.103	0.002

Estimated minimum clinically important difference in 6MWT is 30 meters and in TTSTAND is 0.02 rises/s.[12]

- Safety: No deaths, serious adverse events or study discontinuation related to treatment, Treatment emergent adverse events: cushingoid features (29%), vomiting (14%), vitamin D deficiency (11%), irritability (11%), fall (11%), and weight increase (11%)
    - No significant difference in body mass index between prednisone and vamorolone treated patients
    - Height percentile declined in prednisone-treated (not vamorolone-treated) participants (change from baseline [SD]: prednisone, −1.88 [8.81] percentile vs vamorolone, 6 mg/kg per day, +3.86 [6.16] percentile; P = 0.02).
    - Those treated with vamorolone had a lower rate of bone turnover markers compared to prednisone.

Limitation of this study include a short duration for a long term therapy, narrow age range and functional status (not studied in more progressive disease), only studied in corticosteroid naïve, did not formally test primary efficacy endpoint against active comparator (prednisone) and no direct comparison with other corticosteroids such as deflazacort.

There was a 24 -month phase 2, open-label long-term extension (LTE) study of those who completed a 6-month dose finding study. Corticosteroid naïve boys aged 4.5 to 7.5 years with DMD (N=46) receiving vamorolone were matched and compared with participants receiving other corticosteroids from the Cooperative

International Neuromuscular Research Group Duchenne Natural History Study (CINRG DNHS) and NorthStar United Kingdom (NSUK) Network. Function tests and anthropometric measurements were compared. There was no difference found in NorthStar Ambulatory Assessment (NSAA), BMI or timed function tests (i.e., time to stand velocity, time to climb velocity, time to run or walk 10 meters between participants receiving vamorolone and matched participants in the historical control groups receiving glucocorticoid treatment. Participants in the DNHS experienced growth delay (0.37 percentile/month; 95% CI, 0.23 to 0.52 percentile/month) in comparison with participants treated with vamorolone, who had stable height percentiles.[13,14]

Vamorolone was reviewed by the Oregon Health Authority with the following conclusions[12]:

- compared to placebo vamorolone improved motor function tests (time to stand from supine position, distance walked in six minutes, and mean time to run or walk 10 meters)
- no current evidence one steroid improves muscle function better than another
- vamorolone and prednisone appear to have similar side effects after six months of therapy

Both deflazacort and vamorolone have the potential for the risks associated with chronic use of corticosteroids. Studies indicate that each may have a unique safety profile. There may be lower risk of certain adverse events compared to prednisone such as less weight gain with deflazacort or lower bone turnover and fracture risk with vamorolone. Deflazacort and vamorolone can be a therapeutic alternative when members are experiencing intolerable or concerning side effects from prednisone.

Note to pharmacist if coverage is approved:
For deflazacort, based on individualized dosing, recommend that providers use suspension (rather than tablets) where more cost effective

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14. Smith EC, Conklin LS, Hoffman EP, *et al*; CINRG VBP15 and DNHS Investigators. Efficacy and safety of vamorolone in Duchenne muscular dystrophy: An 18-month interim analysis of a non-randomized open-label extension study. *PLoS Med*. 2020 Sep 21;17(9):e1003222.

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