Treatments for Duchenne Muscular Dystrophy

EOCCO POLICY

Policy Type: PA/ SP Pharmacy Coverage Policy: EOCCO018

Description

Deflazacort (Emflaza) is a corticosteroid prodrug and vamorolone (Agamree) is a dissociative corticosteroid that suppresses the inflammatory pathway. Givinostat (Duvyzat) is a histone deacetylase (HDAC) inhibitor that inhibits HDAC pathological overactivity that results in the cascade of events leading to muscle damage, thereby counteracting the disease pathology, and slowing down muscle deterioration.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
generic deflazacort	6 mg tablets	Duchenne Muscular Dystrophy (DMD)	0.9 mg/kg/day (round to nearest tablet size)
	18 mg tablets		
	30 mg tablets		
	36 mg tablets		
	22.75 mg/mL oral suspension		0.9 mg/kg/day *(see appendix)*
deflazacort (Brand Emflaza)	6 mg tablets		0.9 mg/kg/day (round to nearest tablet size)
	18 mg tablets		
	30 mg tablets		
	36 mg tablets		
	22.75 mg/mL oral suspension		0.9 mg/kg/day *(see appendix)*
vamorolone (Agamree)	40 mg/mL oral suspension		225 mL/30 days
givinostat (Duvyzat)	8.86 mg/mL oral suspension		*Weight based* *(see appendix)*

Initial Evaluation

I. **Generic deflazacort, deflazacort (Brand Emflaza)** and **vamorolone (Agamree)** may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a neuromuscular specialist or neurologist; **AND**
   B. Must not be used in combination with each other for treatment of Duchenne Muscular Dystrophy (DMD); **AND**
   C. A diagnosis of **Duchenne Muscular Dystrophy (DMD)** when the following are met**:**

1. Documentation of DMD gene mutation; **OR**
    i. Documentation of total absence of dystrophin confirmed by muscle biopsy; **AND**
2. Member is two years or older; **AND**
3. Member displays delayed motor milestones (e.g., child not walking by 18 months, toe walking, poor head control, not running by three years old, struggling to hop, abnormal gait, difficulty ambulating without assistance, etc.); **AND**

D. Member's current weight is documented; **AND**
E. Treatment with oral prednisone for six months or greater has been ineffective, not tolerated, or contraindicated ; **AND**
F. Treatment with generic deflazacort has been ineffective, not tolerated, or contraindicated

II. **Givinostat (Duvyzat)** is considered medically necessary when the following criteria below are met:
A. Member is six years or older; **AND**
B. Medication is prescribed by, or in consultation with, a neuromuscular specialist or neurologist; **AND**
C. Medication will not be used in combination with a dystrophin restoration treatment for Duchenne Muscular Dystrophy (e.g., ataluren, Eteplirsen (Exondys 51), Golodirsen (Vyondys 53), Viltolarsen (Viltepso), Casimersen (Amondys 45), delandistrogene moxeparvovec-rokl (Elevidys)); **AND**
D. A diagnosis of **Duchenne Muscular Dystrophy (DMD)** when the following are met**:**
    1. Documentation of DMD gene mutation; **OR**
        i. Documentation of total absence of dystrophin confirmed by muscle biopsy; **AND**
    2. Member displays delayed motor milestones (e.g., child not walking by 18 months, toe walking, poor head control, not running by three years old, struggling to hop, abnormal gait, difficulty ambulating without assistance, etc.); **AND**
E. Member must be ambulatory (e.g., able to walk); **AND**
F. Member is using a corticosteroid concomitantly with givinostat (Duvyzat); **OR**
    1. Treatment with a corticosteroid for six months or greater has been ineffective, not tolerated, or contraindicated; **AND**
G. Member's current weight is documented; **AND**

III. Deflazacort (Emflaza), vamorolone (Agamree), givinostat (Duvyzat) are considered <u>investigational</u> when used for all other conditions, including, but <u>not limited to</u>:
A. Dysferlinopathies: including Miyoshi Myopathy (MM) and limb girdle muscular dystrophy type 2B (LGMD2B)
B. Ulcerative Colitis

C. Myelodysplastic Syndromes: Polycythemia vera
D. Becker muscular dystrophy (BMD)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. The request is for **generic deflazacort, deflazacort (Brand Emflaza), or vamorolone (Agamree)**; **AND**
- Medication requested will not be used in combination with another corticosteroid (e.g., prednisone, deflazacort, etc.); **OR**

IV. The request is for **givinostat (Duvyzat); AND**
- Member must be ambulatory (e.g., able to walk); **AND**
- Medication will not be used in combination with a dystrophin restoration treatment for Duchenne Muscular Dystrophy (e.g., ataluren, Eteplirsen (Exondys 51), Golodirsen (Vyondys 53), Viltolarsen (Viltepso), Casimersen (Amondys 45), delandistrogene moxeparvovec-rokl (Elevidys)); **AND**
- The medication will be used in combination with a steroid unless contraindicated or not tolerated; **AND**

V. Treatment provides clinical benefit to the member, defined as slow or stabilize disease progression in net motor function, compared to pretreatment baseline (e.g., stability or improvement in gait, muscle strength, slowed rate of decline in timed function tests (e.g., 6MWT, 4SC, NSAA, etc.))

Supporting Evidence

I. DMD (Duchenne Muscular Dystrophy) is a rare X-linked genetic disorder characterized by progressive muscle degeneration and weakness due to alterations in DMD genes required to synthesize a protein called dystrophin. Dystrophin is a major component of the cytoskeleton structure that prevents contraction-induced damage. Muscles with low levels of dystrophin are more sensitive to damage, resulting in progressive muscle loss and function. DMD initially presents as developmental delay and weakness in proximal limb muscle in young male s ages three to five years old. Although rare, DMD may affect girls. Due to its gradual progression, if left untreated, most patients with DMD will lose ambulation before the age of 12 years and require noninvasive ventilation. Treatment in DMD target improving motor function, delaying the onset of cardiac and respiratory complications. Given the rarity and complexity of diagnosis and

management of DMD, the treatment of DMD must be initiated by, in or consultation with a neurologist or neuromuscular specialist.

II. Suspected cases of DMD should be referred to a neuromuscular specialist to evaluate creatinine kinase levels. If these are elevated, the diagnosis of DMD should be confirmed by dystrophin genetic testing. In rare cases genetic testing may be negative, but a diagnosis can still be confirmed by a muscle biopsy and dystrophin analysis.

III. There are no curative therapies for DMD. Supportive care is crucial for optimizing health and quality of life for patients with DMD. The 2016 American Academy of Neurology Recommendation on Corticosteroid Use in Duchenne Muscular Dystrophy note that glucocorticoids may be used to improve physical functioning and should be started prior to substantial physical decline. Prednisone and deflazacort have been shown to improve motor and pulmonary function and improve survival. Guidelines have not been updated to include vamorolone (Agamree) or givinostat (Duvyzat).

IV. Per the American Academy of Neurology 2016 Guideline on Corticosteroid Use in Duchenne Muscular Dystrophy:

- Prednisone
    i. Should be offered for improving strength (Level B) and pulmonary function (Level B)
    ii. The preferred dosing regimen of prednisone is 0.75 mg/kg/d (Level B); though this regimen is associated with significant risk of weight gain, hirsutism, and cushingoid appearance (Level B).
    iii. Prednisone 10 mg/kg/weekend is found equally effective at 12 months (Level B).
    iv. Prednisone may be offered for improving timed motor function, reducing the need for scoliosis surgery, and delaying cardiomyopathy onset by 18 years of age (Level C for each).
    v. Retrospective studies and the Duchenne Natural History Study (DNHS) demonstrated that patients with advanced DMD on any steroid regimen for 6 months or greater had significantly longer preserved ambulation.
- Deflazacort
    i. May be offered for improving strength and timed motor function, and delaying age at loss of ambulation (Level C)
    ii. May be offered for improving pulmonary function, reducing the need for scoliosis surgery, delaying cardiomyopathy onset, and increasing survival (Level C for each.)
    iii. Deflazacort (Emflaza) does not provide clinically significant efficacy advantages compared to prednisone, but it is disproportionally more expensive.

- Prednisone and deflazacort are possibly equally effective for improving motor function in patients with DMD. However, there is insufficient evidence to directly compare the effectiveness of prednisone vs deflazacort in cardiac function in patients with DMD.
- Both prednisone and deflazacort have been shown to improve muscle strength compared with placebo.
- There may be differences in weight gain-related adverse events between prednisone and deflazacort.
    i. Central obesity was seen as an adverse event in 25.0% and 24.6% of deflazacort patients compared to 42.9% of prednisone patients and cushingoid appearance was seen in 60.3% and 69.2% of deflazacort patients compared to 77.8% of prednisone patients.

V. There are five gene-based therapies FDA-approved to treat patients with DMD: Eteplirsen (Exondys 51), Golodirsen (Vyondys 53), Viltolarsen (Viltepso), Casimersen (Amondys 45), and delandistrogene moxeparvovec-rokl (Elevidys)). The accelerated approval of all five drugs was based on the surrogate endpoint of an increase in dystrophin production in the skeletal muscle observed in some patients treated with the drugs. However, the amount of dystrophin expression to be translated into a clinical benefit has yet to be established in patients with DMD.

VI. Deflazacort (Emflaza) was evaluated in two multicenter, randomized, double-blind, placebo-controlled trials in 225 patients. Study 1 consisted of 196 male pediatric patients, five to 15 years of age with documented mutation of the dystrophin gene, and onset of weakness before five years of age. The primary endpoint was the average change in muscle strength score between baseline and week 12. The average change was 0.15 (95% CI 0.01, 0.28) and -0.10 (95% CI -0.23, 0.03) for the deflazacort (Emflaza) and placebo groups, respectively. Study 2 consisted of 29 male pediatric patients, six to 12 years of age with documented mutation of the dystrophin gene. The primary endpoint was the average muscle strength score at two years. The results were not statistically significant.

VII. Vamorolone (Agamree) is an FDA approved dissociative steroid indicated for treatment of DMD. Vamorolone (Agamree) is available as a 40mg/mL suspension and dosing is weight-based. Per label, the recommended dose of vamorolone (Agamree) is 6mg/kg, with a max of 300mg daily for those >50kg. A dissociative steroid retains a selective anti-inflammatory profile and assumed to have a favorable side effect profile compared to traditional corticosteroids with reduced bone fragility, metabolic disturbance, and immune suppression.

VIII. Vamorolone (Agamree) was studied in a phase IIb, multicenter, double-blinded, randomized, placebo- and prednisone-controlled trial (VISION-DMD phase IIb) in 121 boys ages ≥ 4 years and <7 years old with confirmed DMD via DMD gene mutation or muscle biopsy. Participants were randomized to receive low or high dose vamorolone (2mg/kg [N=30] or 6mg/kg [N=30]), prednisone (0.75mg/kg [N=30]) or placebo (N=31) daily. Patients that received prior treatment with oral glucocorticoids or other immunosuppressants or clinically significant cardiac disease

were excluded. Baseline characteristics were similar between all groups with a mean age of 5.4 years, weight of 20kg, 82.9% Caucasian, and baseline time to stand (TTSTAND) velocity of 1.7m/s.

IX. The primary endpoint was TTSTAND from supine velocity in the vamorolone 6 mg/kg per day group vs placebo. Treatment with vamorolone 6 mg/kg/day resulted in statistically significant lower TTSTAND scores relative to placebo at week 24, least square mean (LSM) 0.05 m/s in high dose vamorolone compared to -0.01 m/s in the placebo group, LSM difference 0.06m/s, p=0.002 (95% CI, 0.02-0.10). Secondary endpoints included TTSAND velocity in the vamorolone 2mg/kg per day group vs placebo, 6-minute walk test (6MWT) and time to run/walk (TTRW) between high dose vamorolone compared to placebo and low dose vamorolone compared to placebo.

- TTSTAND velocity in the vamorolone 2mg/kg per day 0.03 m/s vs placebo -0.01 m/s, LSM difference 0.05 m/s, p=0.02 (95% CI, 0.01-0.08)
    i. TTSTAND is a validated outcome measure for DMD. A difference of 0.05 m/s in TTSTAND velocity is indicative of clinically meaningful changes. Strength testing is reliable and reflects differences between steroid-treated and naive populations between the ages of 4 and 9 years and for stronger and more mobile subpopulations aged 10 and older. However, strength testing has limited continuity across the entire age range of affected individuals from young children to adults.
- 6MWT in the vamorolone 6mg/kg per day 28.3m vs placebo -13.3m LSM difference 41.6m, p=0.003 (95% CI, 14.2-68.9); vamorolone 2mg/kg per day 23.9 m vs placebo -13.3m, LSM difference 37.1, p=0.009 (95% CI, 9.6-64.7)
- TTRW velocity in the vamorolone 6mg/kg per day 0.26m/s vs placebo 0.01m/s LSM difference 0.024 m/s, p=0.024 (95% CI, 0.09-0.39); vamorolone 2mg/kg per day 0.16 m/s vs placebo 0.01 m/s, LSM difference 0.02 m/s, p>0.05 (95% CI, -0.03-0.28)

X. The number of participants reporting at least one adverse event (AE) was similar between all groups. Participants in the prednisone group experienced linear growth delay, which was not present in the vamorolone group. There were 2 treatment-emergent vertebral fractures at week 24; 1 participant in the prednisone group had a total of 4 incident vertebral fractures, and 1 participant in the placebo group had a single incident vertebral fracture.

XI. The FDA-label for vamorolone (Agamree) has similar warnings and precautions as prednisone and deflazacort (Emflaza). These glucocorticoids have similar safety and efficacy profiles and requiring step through prednisone and generic deflazacort is both clinically appropriate and cost-effective.

XII. Additionally, 41 participants enrolled in a 30-month open label extension trial. Participants were matched and compared with participants from the DNHS. Participants in DNHS were first eligible for inclusion in the control group after they had experienced 6 months of continuous glucocorticoid exposure. There was a decrease in mean TTSTAND velocity from baseline to 30 months (0.206 rises/s vs 0.189 rises/s), which was not a statistically significant change (−0.011

rises/s; CI, −0.068 to 0.046 rises/s). There were no statistically significant differences between participants receiving high dose vamorolone and matched participants in the historical control groups receiving glucocorticoid treatment.

XIII. The clinical program for vamorolone (Agamree) consisted of a moderate to well-designed randomized clinical trial reporting consistent improvement in TTSTAND score, which is an objective, validated measure of muscular function in DMD. Milestones of disease progression, such as loss of ability to rise from floor, ambulate 10 m and self-feed occur in a predictable order, and loss of those abilities can be predicted by timed functional evaluations. The generalizability of current clinical data may be limited due to exclusion of patients with severe disease. However, in the absence of substantial physical decline, vamorolone (Agamree) may provide potential clinical benefit similar to standard of care glucocorticoids.

XIV. Givinostat (Duvyzat) is a histone deacetylase (HDAC) inhibitor, the first oral nonsteroidal drug FDA-approved for all genetic variants of DMD. Although the exact mechanism of HDACs in DMD is still unknown, it is thought that inhibiting HDAC overactivity prevents the cascade of events leading to muscle damage, stabilizing disease progression and slowing down muscle deterioration.

XV. Givinostat (Duvyzat) was evaluated in a randomized, double blind, placebo controlled, multicenter Phase 3 clinical trial (EPIDYS; NCT02851797). The trial enrolled 179 ambulant boys six years of age or older with confirmed DMD and on stable doses of systemic corticosteroids to receive weight-based dosing of givinostat (Duvyzat) or placebo for 18 months. The primary outcome assessed change from baseline in the time to climb 4 standard stairs (4SC) and was complemented by several key secondary endpoints: six-minute walk test (6MWT), North Star Ambulatory Assessment (NSAA), time to rise from floor (TTR), and fat fraction of the vastus lateralis (VL-MFF) measured by magnetic resonance spectroscopy (MRS) which have proven to be sensitive to disease progression in DMD and predictive of loss of ambulation.

XVI. The study met its primary endpoint, and treatment with givinostat (Duvyzat) showed a slower 4SC decline compared to placebo in change from baseline at 18 months (difference vs. placebo of -1.78 seconds, p=0.037). Additionally, secondary endpoints that evaluated muscle function and strength showed favorable results in the givinostat (Duvyzat) -treated group. Givinostat (Duvyzat) treatment was associated with less decline in NSAA total score and item loss, which was nominally significant but not statistically significant, indicating givinostat (Duvyzat) potential to delay disease progression. Givinostat (Duvyzat)-treated participants had a 30% reduction in VLFF compared to the placebo, where VL-MFF is a predictor of loss of ambulation and indicates disease progression in DMD individuals.

XVII. The clinical program for givinostat (Duvyzat) consisted of a moderate quality clinical trial reporting slowed progression in 4SC velocity, which is a validated measure of functional capability in ambulatory patients with DMD. The primary endpoint, 4SC velocity, is a validated endpoint in ambulatory patients where a clinically meaningful change is considered >1 second and a 1.6 second change correlates with a 3-year prolongation in ambulation. Additionally secondary endpoints favor givinostat (Duvyzat) vs placebo, further supporting efficacy. Timed functional evaluations correlate with milestones of disease progression, such as loss of ability to

rise from floor, ambulation, and ability to self-feed. Givinostat (Duvyzat) provides a clinically meaningful change in physical function as evident in supporting secondary outcomes compared to placebo. An ongoing extension study (NCT03373968) is evaluating the long-term safety and efficacy of givinostat (Duvyzat).

XVIII. A greater number of participants in the givinostat (Duvyzat) group (69%) than placebo (28%) had adverse events related to treatment, included diarrhea, abdominal pain, vomiting, decreased platelet counts, and increase in triglycerides. Most adverse events were mild to moderate in severity and were managed by dose reduction or interruption. Vomiting was reported in two participants in the givinostat group as a severe adverse event. Majority of patients completed the study and treatment compliance was high in both groups. There are currently no contraindications to using givinostat (Duvyzat).

XIX. Exposure to treatment with dystrophin restoration agents for DMD (e.g., ataluren, Eteplirsen (Exondys 51), Golodirsen (Vyondys 53), Viltolarsen (Viltepso), Casimersen (Amondys 45), delandistrogene moxeparvovec-rokl (Elevidys) etc.) was excluded from the EPIDYS trial, and the efficacy and safety of combination treatment with givinostat (Duvyzat) has not been evaluated.

XX. Optimal sequencing of DMD gene therapies and use of givinostat (Duvyzat) has not been evaluated. Givinostat (Duvyzat) is not limited to use in any specific DMD variant and could potentially be used in most patients with DMD, including those that previously received gene therapies.

Appendix

I. **Table 1. Recommended dosing of givinostat (Duvyzat)**

Weight (kg)	Dosage	Oral suspension volume	Volume per day supply	# bottles per day supply
10 – 19 kg	2.22 mg twice daily	2.5 mL twice daily	140 mL/28 days	1 bottle/28 days
20 – 39 kg	31 mg twice daily	3.5 mL twice daily	140 mL/20 days	1 bottle/20 days
40 – 59 kg	44.3 mg twice daily	5 mL twice daily	280 mL/28 days	2 bottles/28 days
> 60 kg	53.2 mg twice daily	6 mL twice daily	280 mL/23 days	2 bottles/23 days

- Givinostat (Duvyzat) is available as an 140 mL oral suspension, containing 8.86 mg givinostat per mL. The recommended dosage of givinostat (Duvyzat) is based on body weight and administered orally twice daily with food
- Adverse reactions caused by givinostat (Duvyzat) may necessitate a dosage modification and/or dosage interruption.

II. **Table 2. Recommended dosing of vamorolone (Skyclarys)**

Weight (kg)	Dosage	Oral suspension volume	Volume per 28-day supply	# bottles per day supply
10 – 19 kg	114 mg once daily	3 mL once daily	84 mL	1 bottle/33 days

20 – 39 kg	234 mg once daily	6 mL mg once daily	168 mL	1 bottle/16 days
40 – 45 kg	270 mg once daily	6.75 mL once daily	190 mL	2 bottles/29 days
> 46 kg	300 mg once daily	7.5 mg once daily	210 mL	2 bottles/26 days

- Vamorolone (Agamree) is available as an 100mL oral solution, containing 40mg of vamorolone per mL.
- The recommended dose of vamorolone (Agamree) is 6 mg/kg taken orally once daily, up to a maximum daily dosage of 300 mg for members weighing more than 50 kg (110 lb)

III. **Table 3. Recommended dosing of deflazacort (Emflaza)**

Weight (kg)	Dosage	Oral suspension volume	Volume per 28-day supply	# bottles per day supply
10 – 19 kg	17 mg once daily	0.75 mL once daily	21 mL	2 bottle/34 days
20 – 39 kg	35 mg once daily	1.6 mL mL once daily	45 mL	4 bottles/32 days
40 – 59 kg	53 mg once daily	2.4 mL once daily	68 mL	5 bottles/27 days
> 60 kg	63 mg once daily	2.8 mg once daily	79 mL	6 bottles/27 days

- Deflazacort is available as a 13mL oral solution, containing 22.75mg of deflazacort per mL.
- The recommended dose of deflazacort is weight based, 0.9 mg/kg, and taken orally once daily. In patients who experience intolerable adverse effects, may decrease the dose by 25% to 33%.

Investigational or Not Medically Necessary Uses

I. Dysferlinopathies: including Miyoshi Myopathy (MM) and limb girdle muscular dystrophy type 2B (LGMD2B)
   A. Deflazacort as an ineffective therapy in dysferlinopathies was shown in a double-blinded, placebo-controlled trial. Further evaluation is needed to support use of deflazacort (Emflaza) in this setting.

II. Vamorolone (Agamree) has not been FDA-approved, or sufficiently studied for safety and efficacy for Ulcerative Colitis
   A. There is a withdrawn phase I/II study evaluating the use of vamorolone in pediatric ulcerative colitis.

III. Myelodysplastic Syndromes: Polycythemia vera (PV)

A. Givinostat is currently being studied for the treatment of PV. Results from a phase 1/2 study in 51 patients demonstrated an overall response rate of over 80% throughout a four year follow-up period and an acceptable safety profile; however further evaluation is needed to support the use of givinostat (Duvyzat) in this setting.

IV. Becker muscular dystrophy (BMD)

A. A phase 2 study evaluating givinostat in patients with BMD failed to show significant difference in the primary endpoint compared with placebo. Additionally, treatment with givinostat did not differ in strength assessments or timed-function tests. Givinostat showed a potential signal in slowing progression of BMD via MRI assessment; however MRI results evaluating disease progression in BMD have yet to be translated into a clinical benefit.

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Related Policies

Currently there are no related policies.

Policy Implementation/Update

Action and Summary of Changes	Date
Added ambulatory requirement in renewal. Updated supporting evidence at QL table.	07/2024
Renamed deflazacort and vamorolone policy to "Treatments for Duchenne muscular dystrophy" policy. Added criteria for new medication, givinostat (Duvyzat). Updated QL table, supporting evidence, E/I section, references. Added appendix and related policies.	05/2024
Added step therapy requirement through generic deflazacort for brand vamorolone (Agamree) and brand deflazacort (Emflaza) and updated supporting evidence to reflect required step therapy.	02/2024
Realigned QL table and placed dosage form next to quantity limit. Added vamorolone to QL table Updated initial evaluation to include muscle biopsy and clinical features for diagnosis of DMD. Added vamorolone criteria and investigational condition. Updated supporting evidence.	11/2023
Updated initial approval duration to six months, and QLL box with weight-based dosing. Added requirement for neuromuscular specialist or neurologist. Included requirement for confirmation of diagnosis by genetic testing and addition of member weight to confirm dosing. Requires prednisone be tried and failed for six months to be deemed ineffective or have intolerance. Updated renewal criteria to include requirement for previous approval by Moda and not allowing establishing therapy with samples. Added examples of symptom improvement to renewal criteria.	05/2020
Revised to policy format, include use in pediatric patients down to two years of age.	07/2019
Update to criteria	01/2017
Criteria creation	05/2017