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Policy Number: C10904-A

Emflaza (deflazacort) NC

PRODUCTS AFFECTED

Emflaza (deflazacort)

COVERAGE POLICY

Coverage for services, procedures, medical devices, and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Duchenne muscular dystrophy (DMD)

REQUIRED MEDICAL INFORMATION:
While Emflaza (deflazacort) is indicated for the treatment of DMD, there is insufficient evidence to establish clinical effectiveness or superiority over standard generic prednisone therapy. Emflaza (deflazacort) is considered not medically necessary for all indications, including DMD, due to the limited evidence from published clinical trials and lack of data supporting the long-term benefits and risks associated with deflazacort over prednisone (or other oral corticosteroid such as methylprednisolone, and prednisolone).

Prednisone is the preferred agent in the treatment of DMD as it has been the mainstay of therapy for many years and is the most cost-effective for Molina members.

The use of Emflaza (deflazacort) is considered not medically necessary for the treatment of Duchenne muscular dystrophy (DMD). Molina Healthcare will continue to evaluate and update this policy as relevant clinical evidence becomes available.

- Off-Label Uses: Deflazacort will not be authorized for off-label uses since its application

in other disease states has not been evaluated by the FDA.
- Current or previous access of deflazacort (Emflaza) through importation from outside of the U.S. or by clinical trials are not factors which qualify for neither therapy nor continuation of treatment.
- Pharmaceutical samples: The use of pharmaceutical samples (from the prescriber or manufacturer assistance program) will not be considered when evaluating the medical condition, prior prescription history, or as continuation of therapy.

*FDA-approved indication does not, in itself, dictate coverage. Molina Clinical Policy does not recommend coverage for the FDA-approved indication. Please review this policy in its entirety for indications covered by Molina Healthcare.
This is subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

CONTINUATION OF THERAPY:
N/A

DURATION OF APPROVAL:
N/A

PRESCRIBER REQUIREMENTS:
N/A

AGE RESTRICTIONS:
N/A

QUANTITY:
N/A

PLACE OF ADMINISTRATION:
N/A

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Glucocorticosteroids

FDA-APPROVED USES:
Indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients 2 years of age and older

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
• Warnings and precautions of deflazacort are similar to those of other corticosteroids (eg, prednisone) and include alterations in endocrine function, immunosuppression and increased risk of infection, alterations in cardiovascular/renal function, gastrointestinal perforation, behavioral and mood

disturbances, effects on bones, ophthalmic effects, avoiding certain vaccinations, serious skin rashes, effects on growth and development, myopathy, Kaposi's sarcoma, risk of serious adverse events in infants because of benzyl alcohol preservative, thromboembolic events, and anaphylaxis.

- Common adverse events (AEs) (occurring in >10% of patients compared to placebo at 12 weeks) for deflazacort are similar to those of corticosteroids and include Cushingoid appearance, weight gain, increased appetite, upper respiratory tract infection, cough, pollakiuria, hirsutism, central obesity, and nasopharyngitis.

- Serious AEs associated with deflazacort are also similar to those of corticosteroids and include increase susceptibility to infections, adrenal suppression after prolonged use, Cushing's syndrome, gastrointestinal perforation and bleeding, behavioral and mood changes, reduction in bone mineral density (BMD), ophthalmic effects (cataracts and glaucoma), and negative effects on growth and development [Bello 2015, Biggar 2001, Bonifati 2000, Campbell 2003, Emflaza February 2017, Griggs 2016, McAdam
2012, Parente 2017]

- Specific AEs resulting from use of deflazacort (Emflaza) are serious skin rashes (toxic epidermal necrolysis) reported within 8 weeks of starting treatment (Prescribing Information)

- Deflazacort suspension also includes benzyl alcohol preservative which has been associated with increased risk of serious and fatal reactions in infants and is not approved in children less than 5 years of age [Emflaza (deflazacort) Prescribing Information, 2017]

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Duchenne muscular dystrophy (DMD)

- X-linked recessive neuromuscular disorder resulting in the absence or near-absence of dystrophin protein in muscle cells; leads to muscle damage, loss of physical function, and, ultimately, premature death due to respiratory and/or cardiac failure.
- DMD is the most common and severe form of muscular dystrophy*
  *Muscular dystrophy refers to a group of disorders caused by a mutation in one of several genes required for muscle function. It is classified as Duchenne, Becker, or intermediate type (Darras, 2017).
- No cure for DMD; treatment aimed at managing symptoms and slowing disease progression
- Refer to Appendix 1: Clinical Features and Diagnosis

Glucocorticoids are the mainstay of pharmacologic treatment for DMD

- Standard of care for the treatment of DMD
- Demonstrated to prolong independent ambulation, improve pulmonary function, delay the onset of cardiomyopathy and reduce the incidence of scoliosis
- Both prednisone and deflazacort are corticosteroids listed as standard of care in the management of patients with DMD (Gloss et al. AAN 2016)

Deflazacort

- Granted fast-track approval under the FDA's rare pediatric disease priority review voucher program (FDA, 2016). FDA approved in February 2017 for treatment of DMD in patients ages five and older.
- Deflazacort has been used for decades in Canada (McAdam, Mayo, Alman, & Biggar, 2012) and Europe; however, it had not previously been approved for use in the United States
- Classified as a glucocorticoid prodrug, whose active metabolite has anti-inflammatory and immunosuppressant properties; a methyloxazolone derivative of prednisolone (Biggar 2001,

Patel 2013). Its glucocorticoid potency is 70% to 90% that of prednisolone (Nayak 2008); 1.2 mg of deflazacort is approximately equivalent to 1 mg of prednisone (Biggar 2001).

- The precise mechanism by which deflazacort exerts therapeutic effects in patients with DMD are unknown
- Prior to the FDA approval of Emflaza, there were no other corticosteroids that carried an official indication for the treatment of DMD; however, prednisone has been the mainstay of therapy for quite some time
- Insufficient evidence to support the use for any other indication, including a variety of inflammatory conditions
- Regulatory approval was based on the results of a randomized, placebo-controlled trial (Griggs et al., 2016)
- Efficacy based on 2 clinical trials in males with DMD
    - 1 trial with 196 males aged 5-15 years with documented mutation of the dystrophin gene and onset of weakness before age 5 showed improvements in clinical assessment of muscle strength; stability in average muscle strength maintained through end of study at week 52 in patients treated with deflazacort
    - 1 trial with 29 males showed improvement in average muscle strength and patients receiving deflazacort appeared to lose the ability to walk later compared to placebo

PIVOTAL TRIALS

Efficacy and Safety of Deflazacort vs Prednisone and Placebo for DMD (Griggs RC et al. 2016)

The effectiveness of Emflaza for the treatment of DMD was established in a multicenter, randomized, double-blind, placebo-controlled, 52-week study conducted in the United States and Canada in 1995. Subjects were enrolled from 4 centers in the United States and 5 centers in Canada.

Drug: Deflazacort vs Prednisone vs Placebo

Subjects (n=196) were randomized to therapy with deflazacort, prednisone, or placebo to receive:

- deflazacort 0.9 mg/kg/day (n = 51),
- deflazacort 1.2 mg/kg/day (n = 49),
- prednisone 0.75 mg/kg/day (n = 46), or
- a placebo (n = 50)

Inclusion criteria

- Boys ages 5 to 15, with onset of weakness before age 5
- Increased serum creatine kinase activity at least 10 times the upper limit of normal
- Either genetic analysis of the dystrophin gene or biopsy that demonstrated a clear alteration in dystrophin amount or distribution in the muscle

Exclusion criteria

- Previous long-term use (>1 year) of oral glucocorticoids, active peptic ulcer disease or history of gastrointestinal bleeding or perforation, any use of oral steroids for >1 month within 6 months of study entry, any use of oral steroids for <1 month within 2 months of study entry
- Normal muscle biopsy or muscle biopsy evidence of denervation or glycogen storage disease skin rash suggestive of dermatomyositis

Patient characteristics

- Mean age was 8.8 years, weight was 30.5 kg, height was 131 cm, and body mass index was 17.1 kg/m2; 94.9% of patients were white.

Intervention

In the first phase, patients were randomized to treatment with deflazacort 0.9 mg/kg/day, deflazacort 1.2 mg/kg/day, prednisone 0.75 mg/kg/day, or placebo for 12 weeks. Patients were stratified based on ambulation status and study center. After 12 weeks, the placebo group was re-randomized to 1 of the 3 drug treatment groups for the final 40 weeks, while the other patients continued to receive their study medication for another 40 weeks, for a total of 52 weeks.

- A comparison to placebo was made after 12 weeks of treatment
- After 12 weeks, placebo patients were re-randomized to receive either deflazacort or the active comparator (prednisone)
- All patients continued treatment for an additional 40

weeks Outcomes
- Primary clinical efficacy endpoint: Efficacy was evaluated by assessing the change between Baseline and Week 12 in average strength of 18 muscle groups using a modified Medical Research Council (MRC) index score. Scores are based on several muscle strength assessments and evaluated on a 0 to 11-point rating scale with lower scores indicating more severe disease.
- Secondary outcomes included muscle strength at 1 year, motor function, pulmonary function, disease severity, adverse effects, weight gain and change in growth. Actual MRC scores at baseline, 12 weeks and 1 year were not reported and numbers represent the change in MRC score from baseline.

The approval of deflazacort was based on the Phase III study (Griggs et al.) completed in 1995 however was not published until 2016 because the original study sponsor was purchased by another company that decided not to pursue its development in the United States.

This study provided information regarding how deflazacort compares with another glucocorticoid in the treatment of DMD. It was initially completed in 1995, but the results were never published by the original manufacturer.

CLINICAL EFFICACY SUMMARY
Pivotal Trial (Griggs et al., 2013)
Although the trial was recently published and used to establish FDA approval of deflazacort, it was completed in 1995. Therefore, it may not be generalizable to current treatment such that the study included children with either Duchenne or Becker muscular dystrophy since the distinction between the different types of muscular dystrophy during that time was less clear than it is today. (Griggs et al., 2013) *Discussed in previous section 'Pivotal Trial'
- 7 of the 196 participants were later determined to have Becker muscular dystrophy (instead of DMD) due to a less definitive understanding of the differences between the two diseases at that time.

Cochrane Database Systematic Review (2016)
A Cochrane systematic review concluded that corticosteroids help improve muscle strength and function in the short-term (12 months) and strength for up to 2 years. Because randomized, comparative studies are lacking, it is difficult to recommend one corticosteroid over another. The studies were not of sufficient duration to determine the long-term benefits and risks associated with corticosteroid therapy in patients with DMD. (Matthews E et al. 2016)
Drug Effectiveness Review Project (DERP 2017)
DERP evaluated deflazacort for the treatment of DMD based on 4 randomized controlled trials, 3 systematic reviews, and one guideline. All trials included a similar population of patients (males at least age 5 with DMD), and all compared FDA-approved dosing of deflazacort 0.9 mg/kg/day to prednisone 0.75 mg/kg/day. Overall evidence from these trials was graded as poor quality due to significant methodological flaws and lack of reported data (DERP; Carson S et al. 2017).

Evidence from RCTs was limited by inadequate or unclear methods and lack of adequately reported data. Data suggests that clinical efficacy of prednisone and deflazacort are equivalent, similarly with the side-effect profile. There is no consensus from clinical experts that suggests otherwise. Therefore, additional studies are needed to evaluate comparative safety and adverse effects between deflazacort and other corticosteroids (DERP; Carson S et al. 2017).
- Systematic reviews evaluating adverse effects of deflazacort and prednisone concluded that deflazacort was associated with less weight gain than prednisone from two trials (Bonifati et al., 2000a; Karimzadeh et al. 2012) though the evidence was graded as 'very low quality' indicating very little confidence in the estimated effect (Cochrane Database Syst Review, Matthews et al. 2016).
- In the pivotal study submitted for FDA approval (n=196), patients randomized to deflazacort had less weight gain (5.05 kg) compared to prednisone (8.45 kg; MD 3.4 kg; $p<0.0001$) over the course of 1 year (Griggs et al., 2016). However, incidence of cataracts was higher with deflazacort (6.6%) at 1 year compared to prednisone (4.4%; p-value not reported) (Carson S et al. 2017).

- One study (n=100) reported that more patients on deflazacort developed cataracts compared to patients treated with prednisone (36% vs. 3%, p-value not reported) Reitter (1995); Dubowitz (2000).

Deflazacort was studied against prednisone for the treatment of DMD in 4 RCTs:

- Similar eligibility criteria: boys over 5 years old with a confirmed diagnosis of DMD
- All of the trials included a comparison of deflazacort 0.9 mg/kg/day to prednisone 0.75 mg/kg/day
- The follow-up periods ranged from 12 weeks to 2 years

1) Trial of deflazacort vs. prednisone in boys with DMD or BMD from 1995 [Reiter (1995); Dubowitz (2000)]
N = 100; study duration = 2 years
Reiter (1995) published interim results from 67 boys in 1995 and only presented graphical data without reporting data by intervention group. Dubowitz (2000) presented the results of 100 boys at a conference workshop.
No statistically significant difference in muscle strength (Medical Research Council scale score) or motor outcomes. Data presented graphically only; no differences between groups
Prednisone group had more weight gain (no data) while deflazacort group developed more cataracts (36% vs. 3%), and 20% of enrollees did not complete the study (14 discontinued due to weight gain
Quality Assessment: Poor-quality (randomized controlled trials have clear flaws that could introduce significant bias) (DERP 2017)
Final study results were never fully published. Randomization and allocation concealment methods not reported, baseline characteristics not reported, no detail on blinding (DERP 2017).

2) PIVOTAL TRIAL: Trial of deflazacort vs. prednisone in boys with DMD or BMD from 1995 [Brooke (1996); Griggs (2016)]

- N = 196; study duration = 3 months (primary) and 1 year (other outcomes)
- Both deflazacort and prednisone were significantly more effective than placebo for both muscle strength and motor outcomes. No difference between active groups at 12 weeks or at 1 year.
- Prednisone group had statistically significant weight gain at 1 year (mean difference of 5.05 kg vs 8.45 kg) while deflazacort group developed more cataracts (6.6% vs 4.4%).
- Results of the study were originally presented at the 75thAmerican Academy of Neurology meeting (1996) but were published as part of the FDA clinical review (2016).
- Quality Assessment: Poor-quality (randomized controlled trials have clear flaws that could introduce significant bias) (DERP 2017) Randomization and allocation concealment methods not reported. Only baseline age, race, and BMI reported. No data on disease severity at baseline. Short (12-week) follow-up on primary outcome. Potential conflict of interest: first author is consultant for Marathon pharmaceuticals.
- This study was completed over 20 years ago but just recently published in full.

3) Trial of deflazacort vs. prednisone in boys with DMD from 2000 (Bonifati 2000)

- N = 18; study duration = 2 years
- Double-blind, randomized study of 18 participants for 12 months
- Treatment with 0.75 mg/kg/day prednisone (mean age 7.5 years, range, 5.1 to 10) or 0.9 mg/kg/day deflazacort (mean age 8.6 years, range 5.3 to 14.6)
- Muscle strength: No statistically significant difference in muscle strength using a summed Medical Research Council (MRC) scale score or a summed functional score at 3, 6, or 9 months and results were presented only graphically
- Motor function: No significant differences were found at 3, 6, or 9 months but found statistically significant improvement in functional score at 9 to 12 months with prednisone (but authors attributed to more severe patients dropping out of the study)
- Weight gain: Prednisone group had more weight gain while deflazacort group developed more cataracts. More weight gain was observed in the prednisone group at one year (mean difference

from baseline 2.17 kg vs. 5.08 kg), and continued into the second year (4.6 kg vs. 8.7 kg; p < 0.05)
• Quality Assessment: Poor-quality due to its small sample size and lack of reporting of randomization and allocation concealment methods (DERP 2017). Patients were randomized to prednisone or deflazacort and reportedly stratified by disease severity and age. However, methods used for randomization and allocation concealment were unclear. Authors reported that functional parameters were similar between groups but no data were given. One patient excluded from analysis (6%) (DERP 2017).

4) Trial of deflazacort vs. prednisone in boys with DMD (Karimzadeh 2012)
• N = 34; study duration = 18 months
• Randomized 34 participants to prednisone 0.75 mg/kg/day or deflazacort 0.9 mg/kg/day.
• The report presented limited outcome data at 12 and 18 months. Deflazacort had a statistically significant difference in motor outcomes at 12 months but had no statistically significant difference at 18 months.
• Muscle strength was not evaluated
• Weight gain: Prednisone group had more weight gain at 12 months and 18 months Percent increase in weight at 1 year: 13.0% vs. 21.7% (p = 0.001)
Mean weight gain at 18 months: 21.7% vs. 32.0% (p = 0.046)
• Study had significant loss to follow-up (17.6% deflazacort; 29.4% prednisone) and did not use intent- to-treat analysis
• Authors did not report on randomization, blinding, or baseline characteristics

CLINICAL PRACTICE GUIDELINES
AMERICAN ACADEMY OF NEUROLOGY (AAN)
Practice Guideline Update Summary: Corticosteroid Treatment of Duchenne Muscular Dystrophy: report of the Guideline Development Subcommittee of the American Academy of Neurology (Gloss et al 2016). This guideline was reaffirmed on January 22, 2022.

PRACTICE RECOMMENDATIONS
Deflazacort and prednisone may be equivalent in improving motor function (Level C). There is insufficient evidence to establish a difference in effect on cardiac function (Level U). Prednisone may be associated with increased weight gain in the first years of treatment compared with deflazacort (Level C). Deflazacort may be associated with increased risk of cataracts compared with prednisone (Level C).

The AE profiles of deflazacort and prednisone vary slightly. Weight gain and cushingoid appearance may occur more frequently with prednisone than deflazacort, but cataracts are more frequently reported with deflazacort.
Prednisone (as an intervention for patients with DMD)
• Prednisone 0.75 mg/kg/d has significant benefit in DMD management and should be considered the optimal prednisone dose. Prednisone 10 mg/kg/weekend is equally effective over a 12-month period, although long-term outcomes of this alternate regimen remain to be seen.
• If patients with DMD are treated with prednisone, prednisone 0.75 mg/kg/d should be the preferred dosing regimen (Level B).
• Prednisone 0.3 mg/kg/d may be used as an alternative dosing regimen with lesser efficacy and fewer AEs (Level C). Prednisone 1.5 mg/kg/d is another alternative regimen; it may be equivalent to 0.75 mg/kg/d but may be associated with more AEs (Level C).
• Should be used to improve strength (Level B) and may be used to improve timed motor function (Level C)
• Should be used to improve pulmonary function (Level B)
• May be used to reduce the need for scoliosis surgery (Level C)
• May be used to delay the onset of cardiomyopathy by 18 years of age (Level C)

Deflazacort (as an intervention for patients with DMD)
• Improve strength and timed motor function and delay the age at loss of ambulation by 1.4–2.5

years (Level C)
- Improve pulmonary function (Level C)
- Reduce the need for scoliosis surgery (Level C)
- Delay the onset of cardiomyopathy by 18 years of age (Level C)
- Increase survival at 5 and 15 years of follow-up (Level C)

Data are insufficient to support or refute the following (all Level U)
- The addition of calciferiol and bisphosphonates (alendronate) as significant interventions for improving bone health in patients with DMD taking prednisone
- A benefit of bisphosphonates for improving survival in patients with DMD taking corticosteroids
- A benefit of prednisone for survival
- A significant difference in efficacy or AE rates among daily, alternate day, and intermittent regimens for prednisone or prednisolone dosing
- A preferred dose of deflazacort
- An effect of corticosteroids on quality of life (QoL)

AAN Rating Scheme for the Strength of the Recommendations
A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*
*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2).
B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)
C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)
U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

Reference: Gloss D, Moxley RT, Ashwal S, Oskoui M. Practice guideline update summary: corticosteroid treatment of Duchenne muscular dystrophy: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2016 Feb 2;86(5):465-72. [40 references]

DUCHENNE MUSCULAR DYSTROPHY CARE CONSIDERATIONS WORKING GROUP
Diagnosis and Management of Duchenne Muscular Dystrophy, Part 1: Diagnosis, and Pharmacological and Psychosocial management (Bushby et al 2010)
- Glucocorticoids are the only medications currently available that slow the decline in muscle strength and function in DMD, which in turn reduces the risk of scoliosis and stabilizes pulmonary function. Cardiac function might also improve, with limited data to date indicating a slower decline in echocardiographic measures of cardiac dysfunction, although these measures are not necessarily predictive of the delay in cardiac symptoms, signs, or cardiac-related mortality.
- The goal of the use of glucocorticoids in the ambulatory child is the preservation of ambulation and the minimization of later respiratory, cardiac, and orthopedic complications, taking into account the well-described risks associated with chronic glucocorticoid administration. Particular care needs to be taken with such patients in deciding which glucocorticoid to choose, when to initiate treatment, and how best to monitor the child for any problems.
- No generally accepted guidelines exist in the literature about the best time to initiate glucocorticoid therapy in an ambulatory boy with DMD. The panel's opinion is that the timing of initiation of glucocorticoid therapy must be an individual decision, based on functional state and also considering age and pre-existing risk factors for adverse effects (AEs). Initiation of glucocorticoid treatment is not recommended for a child who is still gaining motor skills, especially when he is under 2 years of age.

• The typical boy with DMD continues to make progress in motor skills until approximately age 4 to 6 years, albeit at a slower rate than his peers. The eventual use of glucocorticoids should be discussed with caregivers at this stage, in anticipation of the plateau in motor skills and subsequent decline. Once the plateau phase has been clearly identified, usually at age 4 to 8 years, the clinician should propose initiation of glucocorticoids unless there are substantial reasons (such as major pre-existing risk factors for AEs) to wait until the decline phase. Starting steroids when in the full decline phase or when ambulation is more marginal is still recommended but might be of more limited benefit.
• Prednisone (prednisolone) and deflazacort are believed to work similarly and neither one has a clearly superior effect on altering the decline in motor, respiratory, or cardiac function in DMD. The choice of which glucocorticoid to use depends on legal availability, cost, formulation, and perceived AE profiles. Prednisone is inexpensive and available in tablet and liquid formulations. Where available, deflazacort is more expensive and comes in fewer tablet sizes. Deflazacort might be preferred to prednisone for some patients because of the likely lower risk of weight gain.

CLINICAL EVIDENCE

Prednisone vs Deflazacort

- According to clinical studies, head-to-head comparisons, and available guidelines for the treatment of individuals with DMD, deflazacort and prednisone appear to have similar efficacy. The selection of one agent over the other may be more dependent on the differences in their respective AE profiles and specifically, on the limited evidence suggesting that deflazacort may be associated with a lesser increase in body weight versus prednisone.
- Prednisone is noted as preferred by experts, however some routinely use deflazacort for DMD and believe it offers a more favorable side effect profile than daily treatment with prednisone, particularly with regard to weight gain (UpToDate, Darras BT) It is noted ‘In most reports, the efficacy of deflazacort for DMD is similar to prednisone (AAN 2016; Bonifati 2000; Balaban B 2015; Markham LW 2005; Griggs RC 2016). These studies reported comparable improvements in muscle function, pulmonary function, and orthopedic outcomes for prednisone and deflazacort treatment. Side effect profiles of prednisone and deflazacort were also similar in most of these reports.’ In one nonrandomized observational study of 340 patients with DMD, deflazacort was associated with a later loss of ambulation and increased frequency of adverse effects (but not weight gain) compared with prednisone/prednisolone (Bello L, 2015).
- Conditions that may be cited by some Prescribers regarding the use of deflazacort over prednisone:
    - Intolerance to prednisone
    - Because deflazacort is a corticosteroid pro-drug, the drug is converted to active corticosteroid in the body, therefore the side effects or intolerance to corticosteroids are also expected with deflazacort
    - FDA labeling of deflazacort includes warnings and precautions for adverse effects associated with corticosteroid use
    - Warnings and precautions of deflazacort are similar to those of other corticosteroids (eg, prednisone) and include alterations in endocrine function, immunosuppression and increased risk of infection, alterations in cardiovascular/renal function, gastrointestinal perforation, behavioral and mood disturbances, effects on bones, ophthalmic effects, avoiding certain vaccinations, serious skin rashes, effects on growth and development, myopathy, Kaposi’s sarcoma, risk of serious adverse events in infants because of benzyl alcohol preservative, thromboembolic events, and anaphylaxis.
    - It has not been determined if switching from one corticosteroid to another improves tolerability. Evidence from RCTs was limited by inadequate or unclear methods and lack of adequately reported data. Data suggests that clinical efficacy of prednisone and deflazacort are equivalent, similarly with the side-effect profile. There is no consensus from clinical experts that suggests otherwise. Therefore, additional studies are needed to evaluate comparative safety and

adverse effects between deflazacort and other corticosteroids.

- Weight gain with prednisone
    - Although there is a potential for less weight gain with deflazacort in the first 12-months, there is no significant difference in weight gain in longer-term use (AAN 2016; Gloss et al.). However, consideration should be given that the recommendations from the AAN guideline are based on non-RCT and lower quality RCT evidence. Therefore, additional evidence and studies are required to support any potential differences.
    - An RCT of 18 patients conducted in Italy was described in two publications reporting outcomes at one year (Bonifati et al., 2000a) and two years (Bonifati et al., 2000b) found deflazacort was associated with less increase in body weight than prednisone after 12 months of therapy (mean difference from baseline 2.17 kg vs. 5.08 kg); however, there was no difference in weight gain with long-term treatment.
        - Outcomes reported at 1 and 2 years included muscle strength, motor outcomes (reported descriptively) and weight gain (Bonifati et al., 2000a; Bonifati et al., 2000b). No difference was observed in muscle strength or functional scores at 2 years. This study was significantly limited by the small sample size, lack of reported outcomes, and significant risk of bias (Carson et al. 2017).
- Muscle Strength
    - According to a systematic review conducted in 2003, deflazacort improves strength and functional outcomes compared with placebo, but information is inadequate to determine whether deflazacort has any benefit over prednisone (Campbell et al. 2003)
    - The randomized controlled trials of deflazacort and prednisone demonstrated no difference in muscle strength and motor outcomes between deflazacort and prednisone for patients with DMD [DERP; (Carson S et al. 2017)].
    - Deflazacort is reported with efficacy similar to prednisone and appears to be effective for the treatment of DMD (AAN 2016, Gloss D et al.; Bonifati et al. 2000; Griggs RC et al. 2016).
    - Studies reported comparable improvements in muscle function, pulmonary function, and orthopedic outcomes for prednisone and deflazacort treatment (Daras BT et al. 2017).
    - A Cochrane systematic review concluded that corticosteroids help improve muscle strength and function in the short-term (12 months) and strength for up to 2 years. Because randomized, comparative studies are lacking, it is difficult to recommend one corticosteroid over another. The studies were not of sufficient duration to determine the long-term benefits and risks associated with corticosteroid therapy in patients with DMD (Matthews et al. 2016).
    - At two neuromuscular centers in Italy, a smaller group of boys with DMD (N=18) were treated with deflazacort 0.9 mg/kg/day or prednisone 0.75 mg/kg/day. The two drugs were considered equally effective at improving motor function and functional performances, but prednisone was associated with a greater increase in weight (Bonifati et al. 2000).

- Insufficient evidence for superiority of deflazacort in clinical trials
    - Based on the available evidence, the safety of deflazacort relative to other therapies is unknown.
    - While deflazacort is indicated for DMD, there is insufficient evidence to establish superiority to prednisone and other oral corticosteroids therapies (including methylprednisolone, and prednisolone) which are cost-effective alternatives available as generics.
    - There is no comparative evidence for deflazacort and prednisone beyond 2 years of use for DMD
    - There is a lack of quality evidence evaluating comparative differences in adverse effects between deflazacort and prednisone. Evidence that deflazacort is associated with significantly less weight gain but more cataracts than prednisone was of insufficient quality. It is also noted that weight gain in patients with DMD is not solely an undesirable side effect because it is associated with an increase in muscle mass (Daras BT et al. 2017).

        - One study reported that ambulatory patients treated with prednisone did not have significantly greater weight gain than placebo treated patients (Backman E. et al.). In contrast, non-ambulatory patients treated with prednisone did have a significantly greater weight gain (Daras BT et al. 2017).
    - Due to significant methodological limitations of these trials and lack of reported data, the true treatment effect may be substantially different from the estimated treatment effect. Two of these RCTs were completed more than 20 years ago, and only one included patients in the United States [(Brooke, 1996; Griggs, 2016); (Reiter, 1995; Dubowitz, 2000)].
    - There is insufficient evidence to evaluate differences in adverse effects between deflazacort and other oral corticosteroids. Evidence is limited by small sample sizes, lack of reported methodology and outcomes, and inadequate data in a United States population of patients.

CLINICAL STUDIES

- The safety and efficacy of deflazacort were demonstrated in 2 pivotal, double-blind, placebo-controlled , multicenter, randomized controlled trials that were conducted in the 1980s and 1990s (Angelini et al 1994, Emflaza Formulary Submission Dossier 2017, Griggs et al 2016)
    - In Study 1 (N = 196), all of the treatment groups (deflazacort 0.9 mg/kg/day or 1.2 mg/kg/day, prednisone 0.75 mg/kg/day) demonstrated statistically significant improvements in muscle strength vs. placebo from BL to Week 12. There were significant increases in weight with prednisone vs. placebo, but no significant differences between the deflazacort groups vs. placebo at Week 12 (Griggs et al 2016).
    - Study 2 (N = 29) failed to yield statistically significant results for the change in muscle strength from BL to Year 2 in patients treated with an alternate regimen of deflazacort (2 mg/kg every other day) or placebo (Angelini et al 1994).
- The FDA approval of deflazacort was based on the Phase III study (Griggs et al.) completed in 1995 but not published until 2016 (the trial was never published by the original manufacturer since it was purchased by another company that decided not to pursue its development in the United States). Therefore, the results of this pivotal trial might not be generalizable to individuals who currently have DMD and may not be generalizable to current treatment when taken into consideration that the study included children with either Duchenne or Becker muscular dystrophy and the distinction between the different types of muscular dystrophy during that time was less clear than it is today (Griggs et al., 2013).
    - 7 of the 196 participants were later determined to have Becker muscular dystrophy (instead of DMD) due to a less definitive understanding of the differences between the two diseases at that time.
- Short-term randomized trials have established that glucocorticoid treatment with prednisone or deflazacort is beneficial for improving function in patients with DMD, but long-term data are scarce. [UpToDate; Darras BT]

  A recent prospective observational study with up to 10 years of follow-up enrolled 440 males with DMD. Compared with glucocorticoid treatment for one month or less, treatment for one year or longer was associated with an increased median age at loss of mobility milestones (by 2.1 to 4.4 years) and upper limb milestones (by 2.8 to 8 years). [McDonald, CM et al 2018]
    - Deflazacort was associated with a significant delay in loss of 3 functional milestones compared with prednisone or prednisolone in a prospective trial (N=440). Patients 2 to 28 years were assessed for 9 milestones (Davis Duchenne Functional Milestones for measuring disease progression) at months 3, 6, 9, 12, 18, 24, and annually thereafter (for 10 years). Age at loss of ability to stand from supine, age at loss of ambulation, and age at loss of hand-to-mouth function with retained hand function were significantly delayed by 2.1 to 2.7 years with deflazacort compared with prednisone or prednisolone therapy. Patients who received cumulative glucocorticoid treatment for 1 year or longer experienced a consistent delayed incidence of

ambulatory disease progression milestones by 2.1 to 4.4 years compared with patients not receiving glucocorticoid therapy or those treated for less than 1 month [McDonald, CM et al 2018]

The Institute for Clinical and Economic Review (ICER) published an Evidence Report assessing the comparative clinical benefit and value of the corticosteroid deflazacort (Emflaza), and two exon-skipping therapies eteplirsen (Exondys 51™) and golodirsen for the treatment DMD. ICER noted: Corticosteroids appear to be effective treatments for DMD patients, potentially increasing muscle strength, improving motor function and delaying loss of ambulation. However, whether there are significant differences in outcomes between patients treated with deflazacort compared with prednisone is less clear, as comparative evidence is limited and potentially confounded. Deflazacort may have greater benefits on motor function and delay of loss of ambulation, although not all data are consistent, and the size of the benefit may be small. The primary interest in deflazacort has been around reduced harms. Most trials reported similar AE rates between deflazacort and prednisone; however, data suggest that deflazacort may cause less weight gain but also reduced growth, increased cataract formation, and increased risk of fracture compared with prednisone. Overall, given the evidence, we have moderate certainty that deflazacort has comparable or better net health benefits compared with prednisone (C+). The rating C+ (comparable or better) reflects a point estimate of either comparable, small, or substantial net health benefit and a lower bound of the conceptual confidence interval that does not extend into the inferior range. (ICER, 2019)

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Emflaza (deflazacort) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Emflaza (deflazacort) include: patients with known hypersensitivity to deflazacort or to any of the inactive ingredients, co- administration with strong (e.g., efavirenz) or moderate (e.g., carbamazepine, phenytoin) CYP3A4 inducers, do not administer live or live attenuated vaccines.

OTHER SPECIAL CONSIDERATIONS:
None

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Emflaza TABS 6MG
Emflaza TABS 18MG
Emflaza TABS 30MG
Emflaza TABS 36MG
Emflaza SUSP 22.75MG/ML

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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Contraindications/Exclusions/Discontinuation	Q4 2023
REVISION- Notable revisions: Place of Administration FDA-Approved Uses Contraindications/Exclusions/Discontinuation References	Q4 2022
Q2 2022 Established tracking in new format	Historical changes on file