Subject: Emflaza (deflazacort)_MEDICAID MEDICAL NECESSITY REVIEW ONLY	**Original Effective Date:** Q2 2020
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DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.

RECOMMENDATIONS

This policy addresses **Emflaza (deflazacort)** for the treatment of **Duchenne muscular dystrophy (DMD)** in patients 5 years and older.

LIMITATIONS/EXCLUSIONS: 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. **Due to 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.

Molina Healthcare will continue to evaluate and update this policy as relevant clinical evidence becomes available.

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

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 (e.g., 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)*.

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]

Institute for Clinical and Economic Review (ICER), published an Evidence Report assessing the comparative clinical benefit and value of the corticosteroid deflazacort, 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)

FDA INDICATIONS

Duchenne Muscular Dystrophy (DMD) Treatment of Duchenne muscular dystrophy (DMD) in patients ≥2 years of age

Available as: Deflazacort is available as an immediate-release tablet and an oral suspension.

- Tablets: 6 mg, 18 mg, 30 mg, and 36 mg
- Oral suspension: contains 22.75 mg/mL. Supplied in a 20 mL bottle containing 13 mL of drug suspension. *Deflazacort oral suspension contains benzyl alcohol (10.45 mg/mL). Serious and fatal adverse reactions including "gasping syndrome" can occur in neonates and low birth weight infants treated with benzyl-alcohol preserved drugs. The "gasping syndrome" is characterized by central nervous system depression, metabolic acidosis, and gasping respirations. Consider the combined daily metabolic load of benzyl alcohol from all sources when prescribing deflazacort. The minimum amount of benzyl alcohol at which serious adverse reactions can occur is not known. At the recommended dose of deflazacort, patients would receive approximately 0.4 mg/kg/day of benzyl alcohol.*

FDA Approved: February 2017; Deflazacort has been on the market in Europe and Canada for decades, but only recently achieved FDA approval in the United States in February 2017.

- Orphan drug designation: Treatment of DMD
- Orphan drug designation: Treatment of pediatric (ages 0 through 16) juvenile idiopathic arthritis (JIA) International League of Associations for Rheumatology (ILAR) categories excluding systemic JIA

Black Box Warnings/REMS: *None at the time of this writing*

CLASSIFICATION: Musculoskeletal Anti-inflammatory Agents; Corticosteroids

COVERAGE CRITERIA FOR INITIAL AUTHORIZATION

Emflaza (deflazacort) for the treatment of Duchenne Muscular Dystrophy (DMD) may be authorized for members who meet **ALL** the following criteria **[ALL]**

1. Prescriber specialty [ONE]

- ❒ Prescribed by, or in consultation with, a board-certified neurologist, neuromuscular disorder specialist, or physician experienced in the treatment of Duchenne Muscular Dystrophy (DMD). Submit consultation notes if applicable.

  NOTE: Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

2. Diagnosis/Indication [ALL]

Documentation of ALL the following criteria are required. May include chart notes from the member's medical records, relevant labs and/or tests, and other relevant clinical information supporting the diagnosis

- ❒ Diagnosis of Duchenne muscular dystrophy (DMD) confirmed by ONE of the following. Documentation required: [ONE]
  - ❍ Genetic testing (e.g., dystrophin deletion or duplication mutation found)
    OR
  - ❍ Absence of dystrophin protein confirmed by muscle biopsy
    - ◆ *Skeletal muscle biopsy and analysis of dystrophin expression if genetic testing does not identify pathogenic variant*

- ❒ Baseline motor milestone score from ONE (1) the following assessments:
  - ❍ 6-minute walk test (6MWT)
  - ❍ North Star Ambulatory Assessment (NSAA)
  - ❍ Motor Function Measure (MFM)
  - ❍ Hammersmith Functional Motor Scale (HFMS)

  NOTE: Reauthorization requires positive response to therapy from the same baseline motor milestone score

3. Age/Gender/Restrictions [ALL]

- ❒ 2 years of age or older
  - ◆ *Safety and effectiveness in pediatric patients below the age of 2 years have not been established.*

- ❒ Baseline ophthalmology exam. Documentation required. **NOTE:** Follow-up required at least annually.

4. Conventional Therapy/Concurrent Therapy/Other Requirements [ALL]

- ❒ Member experienced clinically significant adverse effects on prednisone. Documentation required. [ONE]
  - ❍ Cushingoid appearance; **OR**
  - ❍ Central (truncal) obesity; **OR**
  - ❍ Undesirable weight gain, defined as ≥ 10% of body weight gain increase over a 6-month period; **OR**
  - ❍ Diabetes and/or hypertension that is difficult to manage per the prescribing physician; **OR**
  - ❍ Neuropsychiatric side effects (abnormal behavior, aggression) while on prednisone therapy, that has or would require a prednisone dose reduction

- ❒ Absence of active infection [i.e. active ocular herpes simplex, tuberculosis or Hepatitis B virus (HBV)]. If member has a history of HBV infection, Prescriber agrees to monitor for HBV reinfection.
  - *Close observation is required in patients with latent tuberculosis (TB) and/or TB reactivity; restrict use in active TB (only in conjunction with antituberculosis treatment). Hepatitis B reactivation can occur in patients who are hepatitis B carriers.*

- ❒ Emflaza will NOT be given concurrently with live vaccinations
  NOTE: Any live-attenuated or live vaccines should be administered at least 4 to 6 weeks prior to starting deflazacort. **Molina Clinical Reviewer: Review member's vaccine schedule in accordance to age.**

5. Contraindications*/Exclusions/Discontinuations

**Emflaza (deflazacort) carries no black box warnings or contraindications in the FDA-approved labeling*

Authorization will not be granted if ANY of the following conditions apply [ANY]

- ❒ Non-FDA approved indications
- ❒ Hypersensitivity to Emflaza (deflazacort) or to any of the inactive ingredients (tablets: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, and pre-gelatinized corn starch; suspension: acetic acid, aluminum magnesium silicate, benzyl alcohol, carboxymethylcellulose sodium, polysorbate 80, purified water, and sorbitol)

Exclusions

- ❒ Concurrent administration with live vaccinations
- ❒ Moderate or strong CYP3A4 inducers in the last 90 days (e.g. bexarotene, carbamazepine, modafinil, nevirapine, phenobarbital, phenytoin, pioglitazone, primidone, rifabutin, rifampin, rifampin-isoniazid, rifampin-isoniazid-pyrazinamide, efavirenz, dabrafenib, bosentan, enzalutamide). Documentation required. NOTE: List is not all inclusive. [MOLINA CLINICAL REVIEWER: Review claims history]

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful but are not sufficient documentation unless ALL specific information required by this MCP is included.

- ❒ Member's recent weight (within the past 30 days) must be provided to calculate weight-based dose for authorization

NOTE: *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.*

REAUTHORIZATION /CONTINUATION OF THERAPY

Continuation of therapy with Emflaza (deflazacort) may be authorized for members who meet **ALL** the following criteria **[ALL]**

1. Initial Coverage Criteria

- ❑ Member currently meets ALL initial coverage criteria

2. Adherence to Therapy/Compliance

- ❒ Adherence to therapy at least 85% of the time as confirmed by Prescriber or member's claims history **NOTE:** Therapy may be discontinued due to poor adherence upon recommendation of the Molina Medical Director when adherence < 85% has been demonstrated in at least two months during the course of therapy

- ❒ Absence of unacceptable adverse effects or complications from Emflaza (deflazacort)

3. Labs/Reports/Documentation required [ALL]

- ❒ Positive response to therapy confirmed by stabilization, or less than expected decline, in baseline motor milestone score from ONE (1) the following assessments*: [ONE]
  - ❍ 6-minute walk test (6MWT)
  - ❍ North Star Ambulatory Assessment (NSAA)
  - ❍ Motor Function Measure (MFM)
  - ❍ Hammersmith Functional Motor Scale (HFMS)

  *Prescriber may submit additional supporting documentation of objective assessment of ambulation or other muscle function, including pulmonary or cardiac function. This may include improvement in muscle strength tests (e.g., Medical Research Council [MRC] scale for muscle strength with 0 being no movement and 5 being normal strength), Pulmonary function tests (e.g., forced vital capacity [FVC] and maximal expiratory pressure), Timed functional tests (e.g., standing from lying position, climbing 4 stairs, running/walking 30 feet, propelling a wheelchair 30 feet)

- ❒ Documentation of improvement in the symptom(s) or side effect(s) associated with prednisone use has improved with Emflaza, *including but not limited to*:
  - ❍ If neuropsychiatric side effects while on prednisone, member has shown improvement in neuropsychiatric symptoms
  - ❍ If excessive weight gain with prednisone, member has experienced a return to baseline growth curve expectations or remained on the same
    - *American Academy of Pediatrics/CDC Weight for Age Growth Chart: https://www.cdc.gov/growthcharts/data/set1clinical/cj41c021.pdf*

- ❒ Evaluation by an ophthalmologist for development of deflazacort-related adverse effects (e.g., cataracts) after initiation of deflazacort (required annually). Documentation required.
  - *Prolonged use may cause posterior subcapsular cataracts, glaucoma (with possible nerve damage), and increased intraocular pressure.*

4. Discontinuation of Treatment

- ❒ Intolerable adverse effects or drug toxicity (*not an all-inclusive list*): Serious skin rashes, behavioral and mood disturbances, ophthalmic effects (cataracts, infections, and glaucoma); hematologic abnormalities, Cushingoid appearance, upper respiratory tract infection

- ❒ Contraindications/Exclusions to therapy [ANY]
  Authorization will not be granted if ANY of the following conditions apply [ANY]
  - ❍ Non-FDA approved indications
  - ❍ Hypersensitivity to Emflaza (deflazacort) or to any of the inactive ingredients (tablets: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, and pre-gelatinized corn starch; suspension: acetic acid, aluminum magnesium silicate, benzyl alcohol, carboxymethylcellulose sodium, polysorbate 80, purified water, and sorbitol)

  Exclusions
  - ❍ Concurrent administration with live vaccinations
  - ❍ Moderate or strong CYP3A4 inducers in the last 90 days (e.g. bexarotene, carbamazepine, modafinil, nevirapine, phenobarbital, phenytoin, pioglitazone, primidone, rifabutin, rifampin, rifampin-isoniazid, rifampin-isoniazid-pyrazinamide, efavirenz, dabrafenib, bosentan, enzalutamide). Documentation required. NOTE: List is not all inclusive. [MOLINA CLINICAL REVIEWER: Review claims history]

5. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful but are not sufficient documentation unless ALL specific information required by this MCP is included.

- ❒ Member's recent weight (within the past 30 days) must be provided to calculate weight-based dose for authorization

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and monitoring.

1. Recommended Dosage [ALL]

- ❒ 0.9 mg/kg once daily
  - *CYP3A4 Inhibitors (e.g., clarithromycin, fluconazole, diltiazem, verapamil): Administer 1/3 of the recommended dosage when administered with moderate or strong CYP3A4 inhibitors.*
  - *CYP3A4 Inducers: Avoid use with moderate or strong CYP3A4 inducers*

2. Authorization Limit [ALL]

- ❒ Quantity limit: Dose does not exceed 0.9 mg/kg/day. Dosage will be achieved using the fewest number of tablets (or volume of solution) per day.
- ❒ Duration of therapy [AS APPLICABLE]
  - ❍ Initial Therapy: May authorize up to 6 months of initial therapy
  - ❍ Continuation of therapy: May be authorized for up to 12 months. Subsequent approval will be based on continuous progress notes from the Prescriber documenting improvement from baseline.

3. Route of Administration [ALL]

- ❒ Medication is considered self-administered until information from the manufacturer, scientific literature, practice standards, or governing State or Federal agency indicates self-administration is not safe or acceptable.
- ❒ Refer to Specialty Medication Administration Site of Care Policy P&P: MHI Pharm 11
- ❒ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare.

COVERAGE EXCLUSIONS

This policy addresses Emflaza (deflazacort) for the treatment of Duchenne Muscular Dystrophy (DMD) in patients 5 years and older when appropriate criteria are met.

All other uses of Emflaza (deflazacort) that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy is considered not medically necessary. This is subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

BACKGROUND/SUMMARY OF EVIDENCE

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/m^2; 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.

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)

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.**

APPENDIX

Appendix 1: Duchenne Muscular Dystrophy (DMD)

Muscular dystrophy includes a group of genetic disorders that cause muscle weakness and progressive disability. Duchenne muscular dystrophy (DMD) is the most common and progresses most rapidly.

Duchenne muscular dystrophy (DMD)

- A rare genetic disorder characterized by progressive muscle deterioration and weakness
- An X-chromosome-linked disease recessive disorder caused by mutations (mainly deletions) in the dystrophin gene that lead to an absence or defect in the dystrophin protein (a protein that that protects

muscles from deterioration). Dystrophin is essential for maintenance of myocyte integrity and helps keep muscle cells intact. Dystrophin is located primarily in skeletal and heart muscle.

- As males have only one X chromosome, and therefore one single copy of the dystrophin gene, they have a much higher probability of developing DMD. A small number of females are also affected but remain asymptomatic and only rarely present with a mild form of the disease.
- The most common type of muscular dystrophy; DMD is caused by an absence of dystrophin, a protein that helps keep muscle cells intact
- Based on population studies, the prevalence of DMD in the US is estimated to be 0.4 per 10,000 males, resulting in approximately 6,000 affected people in the US (Romitti, 2015)
- Associated with complete inability to produce functional dystrophin protein
- Affected children with DMD typically develop symptoms in early childhood around 3-5 years old, experiencing progressive muscle weakness and deterioration. Patients with DMD progressively lose the ability to perform activities independently and usually become non-ambulatory by their early teenage years and require the use of a wheelchair.
- As the disease progresses, life-threatening heart and respiratory conditions can occur. Patients typically succumb to the disease in their 20s or 30s; however, disease severity and life expectancy vary.
- In absence of treatment, the patient experiences:
  - wheelchair dependence before age 13 years
  - death occurs by, or around, age 20 years

Prognosis of DMD

- Death occurs around age 20 in absence of treatment and is usually due to cardiac or respiratory failure
- Disease progression in patients with DMD
  - Scoliosis is frequent after loss of ambulation
  - Risk for cardiomyopathy increases with age in absence of ventilatory intervention

Treatment Overview: Pharmacologic Agents/Conventional Therapy

There is no curative therapy, but management of disease manifestations can prolong survival and improve quality of life. A multidisciplinary team is required for management of patient with DMD and treatment options for DMD predominantly focus on management of symptoms and secondary complications.

<u>Goals of management for DMD</u>

- Preserve strength, ambulation, and ventilatory and cardiac function
- Minimize of steroid complications where applicable
- Prevent and treat complications including contractures, scoliosis, ventilatory function impairment or failure, and cardiomyopathy
- Determine and arrange appropriate school environment and manage family stressors

Other pharmacologic therapies for DMD are primarily aimed at the management of comorbidities such as cardiomyopathy, osteoporosis, pain management, and respiratory failure. These treatment options include angiotensin-converting-enzyme (ACE) inhibitors, beta-blockers, calcium and vitamin D supplements, muscle relaxants, and non-steroidal anti-inflammatory drugs.

- Corticosteroids
  - DMD Care Considerations Working Group consensus guidelines urge consideration of glucocorticoid therapy (prednisone or deflazacort) for all patients with DMD (optimal dose ranges not established)
    - Goal in the ambulatory child is to preserve ambulation and minimize later respiratory, cardiac, and orthopedic complications
    - Goal of continuing glucocorticoid therapy after loss of ambulation is to preserve upper limb strength, reduce scoliosis progression, and delay declines in respiratory and cardiac function

- Generally used to preserve ambulation and minimize complications in patients with DMD
  - In ambulatory patients, recommended if motor skills have plateaued or begun to decline
  - In non-ambulatory patients, glucocorticoids often continued if already started while ambulatory, but limited evidence regarding starting glucocorticoids
  - Daily dosing preferred over alternative regimens (alternate day, high-dose weekend, or 10-day cycles)
  - Monitor and manage side effects associated with chronic steroid therapy
- Vitamin D and calcium supplementation suggested to manage bone health in patients with DMD
- Respiratory care including airway clearance techniques, nocturnal ventilatory support, daytime non-invasive ventilation, and tracheostomy may be indicated/desired as disease progresses
- For management of cardiac dysfunction, consider:
  - Diuretics, angiotensin-converting enzyme (ACE) inhibitors, and/or beta blockers to treat manifestations of cardiac dysfunction
  - Anticoagulation therapy in patients with severe cardiac dysfunction to prevent systemic thromboembolic events

Appendix 2: Guidelines

American Academy of Neurology guideline update on corticosteroid treatment of Duchenne dystrophy can be found in Neurology 2016 Feb 2;86(5):465 or at National Guideline Clearinghouse 2016 Jun 6:50008

American Academy of Pediatrics (AAP) policy statement on cardiovascular health supervision for individuals affected by Duchenne or Becker muscular dystrophy can be found in Pediatrics 2005 Dec;116(6):1569 full-text, reaffirmed 2008 Dec, commentary can be found in Pediatrics 2006 May;117(5):1864 full-text

United States expert consensus guideline on diagnosis and management of Duchenne muscular dystrophy

- Part 1: Diagnosis, pharmacological and psychosocial management can be found in Lancet Neurol 2010 Jan;9(1):77 PDF or at National Guideline Clearinghouse 2010 Aug 2:15644
- Part 2: Implementation of multidisciplinary care can be found in Lancet Neurol 2010 Feb;9(2):177 PDF or at National Guideline Clearinghouse 2010 Aug 2:15645

Appendix 3: Warnings and Precautions for Adverse Effects of Corticosteroids

- 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]

CODING INFORMATION: THE CODES LISTED IN THIS CLINICAL POLICY ARE FOR INFORMATIONAL PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE AND INCLUSION OR EXCLUSION OF ANY CODES DOES NOT GUARANTEE COVERAGE. PROVIDERS SHOULD REFERENCE THE MOST UP-TO-DATE SOURCES OF PROFESSIONAL CODING GUIDANCE PRIOR TO THE SUBMISSION OF CLAIMS FOR REIMBURSEMENT OF COVERED SERVICES.

CPT	Description

HCPCS	Description
J3490	Unclassified drugs

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Reviews, Revisions, and Approvals	Approval
Policy Developed Peer Review: AMR Peer Review Network. 2/25/2020. Practicing Physician. Board certified in Neurology, Sleep Medicine	P&T Q2 2020

Policy Revision Minor revisions; clarifications to existing criteria with verbiage and placement; no change to intent. Revised duration of approval from 3 months (initial) and 6 months (continuation) to 6 months and 12 months	P&T Q4 2020

**All content, clinical evidence, coverage criteria, practice guidelines, appendices and reference sections reviewed and revised with the most recent medical literature and available evidence for both 'Annual Reviews' and 'Policy Revisions.' Annual Reviews without notable changes to coverage criteria or position may not require Peer Review. Policy Revisions include notable content updates or revisions that which may have affected criteria or requires review by a practicing specialist, Peer Reviewer.*