Medication Policy Manual

Topic: Emflaza™, deflazacort

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Committee Approval Date: February 17, 2017

Next Review Date: February 2018

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IMPORTANT REMINDER
This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description
Deflazacort (Emflaza) is an oral medication that may be used to treat Duchenne muscular dystrophy (DMD). Deflazacort (Emflaza) is a corticosteroid prodrug, which converts to active corticosteroid in the body. Corticosteroids decrease inflammation and suppress the immune system. It is unknown exactly how deflazacort (Emflaza) works for patients with DMD. It is also unknown if deflazacort (Emflaza) is safer or more effective than prednisone, a low-cost generic corticosteroid.
Policy/Criteria

I. Most contracts require prior authorization approval of deflazacort (Emflaza) prior to coverage. The use of deflazacort (Emflaza) is considered not medically necessary when used for Duchenne muscular dystrophy (DMD).

II. Deflazacort (Emflaza) is considered investigational when used for all other conditions, including but not limited to the following:

A. Allergic conjunctivitis
B. Cystoid macular edema with Retinitis Pigmentosa,
C. Dysferlinopathy.
D. Epilepsy
E. Giant cell arteritis (GCA)
F. Inflammatory arthropathies (not otherwise specified)
G. Idiopathic (autoimmune) thrombocytopenic purpura (ITP)
H. Juvenile rheumatoid (idiopathic) arthritis (JRA, JIA)
I. Nephrotic syndrome
J. Polymyalgia rheumatica (PMR)
K. Rheumatoid arthritis (RA)
L. Sarcoidosis
M. Solid organ transplant (such as kidney, heart transplant)
N. Systemic lupus erythematosus (SLE)
O. Urolithiasis (ureteral stones)

Position Statement

- Corticosteroids, including deflazacort (Emflaza), are effective in the management of Duchenne muscular dystrophy (DMD). For many years, prednisone has been considered the standard of care corticosteroid in the U.S. for treatment of DMD.
- Other commercial available oral corticosteroids include prednisone, methylprednisolone, and prednisolone, and all available as much lower-cost generics.
- Although deflazacort (Emflaza) is FDA approved for DMD, there is insufficient evidence to establish superiority to much less costly alternatives, such as standard generic prednisone therapy. Therefore the use of deflazacort (Emflaza) for DMD is considered not medically necessary.
- Since deflazacort (Emflaza) is a corticosteroid prodrug, the warnings of deflazacort (Emflaza) use are similar to those found with other corticosteroids, such as high blood sugars, weight gain, immunosuppression, mood swings, and reduction in bone mineral density (BMD).
- Side effects or intolerance to generic corticosteroids are largely expected with the use of deflazacort (Emflaza) given the medication is converted to active corticosteroid in the body. It is unknown that switching from one corticosteroid to another improves tolerability.
- In addition, there is insufficient evidence for superiority of deflazacort (Emflaza) in clinical trials. Based on the available evidence, the safety of deflazacort (Emflaza) relative to other therapies is unknown at this time.
- There is insufficient evidence to support the use of deflazacort (Emflaza) for any other indication, including a variety of inflammatory conditions.

Clinical Efficacy

There is moderate certainty that corticosteroids are safe and effective in the management of patients with Duchenne muscular dystrophy (DMD).
- A high-quality Cochrane systematic review concluded that corticosteroids, including deflazacort (Emflaza), improve muscle function and strength. There was no evidence from randomized controlled trials (RCTs) to conclude long-term benefits, such as prolongation of ambulation or delay to loss of ambulation (LoA). The systematic review included the two pivotal trials used by the FDA for the approval of deflazacort (Emflaza).
  - One small two-year placebo-controlled trial (n=28) showed improved muscle strength for up to two years with deflazacort (Emflaza) versus placebo; however, the Cochrane authors stated the trial was of very low quality such that no conclusions can be made based on these findings. Less than half of the randomized subjects were evaluable for the 2-year endpoint. In addition, the trial used dosing significantly different from that in the FDA labeling (2 mg/kg doses every other day vs. FDA-approved 0.9 mg/kg/day).
  - One larger 12-month trial (n=196) showed improved muscle strength with deflazacort (Emflaza) (0.9 mg/kg/day or 1.2 mg/kg/day) versus placebo, but similarly to prednisone 0.75 mg/kg/day.
    - Only the abstract data was evaluable for the Cochrane review (Feb. 2016).
    - In November 2016, prior to the FDA approval of deflazacort (Emflaza), the trial was published in full, with similar efficacy conclusions. Both doses of deflazacort (Emflaza) and prednisone significantly improved muscle strength versus placebo. Of note, there were no statistical comparisons of the relative efficacy of prednisone with either dose of deflazacort (Emflaza).
- Two recent longer-term observational trials support the efficacy of corticosteroids for long term use in DMD. However, specific conclusions as to the benefits of therapy are limited by the lower quality of this non-controlled trial evidence.
- Both prednisone and deflazacort (Emflaza) are recognized by the American Academy of Neurology (AAN) and US Centers for Disease Control and Prevention (CDC) clinical practice guidelines as effective options in the management of patients with DMD. Both guidelines recognize the potential different adverse event profiles between deflazacort (Emflaza) and prednisone, based on lower quality evidence.
* In particular, behavioral issues may be problematic with prednisone. Modification of dosing to after school hours or use of a high-dose weekend schedule (prednisone 5mg/kg on Friday and Saturday) may be an option.

* The AAN guidelines note a potential for less weight gain with deflazacort (Emflaza) in the first 12-months, but no significant difference in weight gain in longer term use. However, the recommendations are based on non-RCT and lower quality RCT evidence. More evidence is needed to clarify any potential differences.

* Perceived side-effect profiles are noted to be a factor in choice of corticosteroid. [9]

- Given the lack of superior benefit as compared to much less costly options, the use of deflazacort (Emflaza) is considered not medically necessary when used for DMD. Although DMD is an FDA-approved indication for deflazacort (Emflaza), generic corticosteroids, such as prednisone, are less costly alternatives and appear to be equally effective.

**Other indications**

- There is insufficient evidence for the use of deflazacort (Emflaza) in other indications, including, but not limited to, allergic conjunctivitis, cystoid macular edema with retinitis pigmentosa, dysferlinopathy, epilepsy, giant cell arteritis (GCA), inflammatory arthropathies (not otherwise specified), idiopathic (autoimmune) thrombocytopenic purpura (ITP), juvenile rheumatoid (idiopathic) arthritis (JRA/JIA), nephrotic syndrome (idiopathic), polymyalgia rheumatica (PMR), rheumatoid arthritis (RA), sarcoidosis, solid organ transplant (such as kidney or heart transplant), systemic lupus erythematosus (SLE), ureteral stones, and urolithiasis. The evidence is limited to pilot trials and small randomized controlled trials with less than 25 patients per treatment arm. [10-33] Additional evidence (larger randomized controlled trials) is needed to establish the safety and efficacy of deflazacort (Emflaza) in these conditions, as well as any superiority to other available corticosteroids. Most of the trials did not include comparison to standard of care generic corticosteroids, such as prednisone or methylprednisolone.

**Safety**

- There is a substantial track-record of marketing experience over 10 years with deflazacort (Emflaza) in Europe and Canada. [1]

- However, there is insufficient evidence to establish a superior adverse event profile for deflazacort (Emflaza) as compared to the many other available lower cost corticosteroids. Although several trials evaluated the effects of deflazacort (Emflaza) on bone mineral density, blood glucose, or weight gain, the small size of individual trials limits conclusion of any conclusive superiority of deflazacort (Emflaza). [10-33]

- Weight gain
The AAN guidelines indicate some potential for superior tolerability with deflazacort (Emflaza) as compared to prednisone. However, the recommendation is based on very low quality, non-randomized controlled trial evidence. The guideline also notes a potential for less weight gain with deflazacort (Emflaza) in the first 12-months, but no significant difference in weight gain in longer term use as compared to prednisone.

The pivotal Phase 3 trial for the approval of deflazacort (Emflaza) evaluated the difference in weight gain between deflazacort (Emflaza) and prednisone. However, the evidence is limited to 12-month data, which limits conclusion of any superiority of either corticosteroid for long-term weight gain.

All other evidence regarding relative weight gain is from lower quality evidence, mostly non-RCT data (retrospective, observational) with inconsistent results. One larger observational cohort (n=340) found no difference in weight gain between deflazacort (Emflaza) and prednisone, but noted variety of dosing regimens limits a conclusive comparison. A smaller retrospective analysis (n=97) found 86% of patients had normal weight velocity with long-term steroids (mean of 8.5 years) but did not compare weight gain between deflazacort (Emflaza) and prednisone.

More evidence is needed to clarify any potential differences. Use of nutritional counseling for a low-glycemic diet and appropriate calorie intake is recommended.

- Common adverse events (AEs) for deflazacort (Emflaza) are similar to those of corticosteroids and include Cushingoid appearance, weight increased, increased appetite, upper respiratory tract infection, cough, pollakiuria, hirsutism, central obesity, and nasopharyngitis.

- All of these are known common AEs for corticosteroids, along with impaired sugar tolerance, high blood sugars.

- Serious adverse events associated with deflazacort (Emflaza) 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.

- Specific adverse reactions resulting from use of deflazacort (Emflaza) are serious skin rashes (toxic epidermal necrolysis) reported within 8 weeks of starting treatment.

**Cross References**

Eteplirsen for Duchenne Muscular Dystrophy, BlueCross BlueShield Association Medical Policy, 5.01.27, Issue December 2016.

Exondys 51™, eteplirsen, Medication Policy Manual, Policy No. dru480
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**References**


**Revision History**

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<td>2/17/2017</td>
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