Emflaza (deflazacort)

Policy Number: 5.01.626  Last Review: 06/2017
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Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Emflaza when it is determined to be medically necessary because the following criteria have been met.

When Policy Topic is covered
Emflaza may be considered medically necessary when the following criteria (A, B, and C) are met:

A. Patient has a diagnosis of Duchenne muscular dystrophy; AND
B. Patient is at least 5 years of age; AND
C. Patient meets one of the following conditions (I or II):
   I. Patient has tried generic prednisone for \( \geq \) 6 months AND according to the prescribing physician, the patient has had at least one of the following significant intolerable adverse effects (AEs) [a, b, c, or d]:
      a) Cushingoid appearance; OR
      b) Central (truncal) obesity; OR
      c) Undesirable weight gain defined as a \( \geq \) 10% of body weight gain increase over a 6-month period; OR
      d) Diabetes and/or hypertension that is difficult to manage according to the prescribing physician; OR
   II. According to the prescribing physician, the patient has experienced a severe behavioral AE while on generic prednisone therapy that has or would require a prednisone dose reduction.

When Policy Topic is not covered
Emflaza is considered investigational when used for all other indications 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)
Considerations
Emflaza requires prior authorization through the Clinical Pharmacy Department.

This Blue Cross and Blue Shield of Kansas City policy Statement was developed using available resources such as, but not limited to: Food and Drug Administration (FDA) approvals, Facts and Comparisons, National specialty guidelines, Local medical policies of other health plans, Medicare (CMS), Local providers.

Description of Procedure or Service
Deflazacort (Emflaza) is an oral medication that may be used to treat 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.

Rationale
Corticosteroids, including deflazacort (Emflaza), are effective in the management of DMD. For many years, prednisone has been considered the standard of care corticosteroid in the U.S. for treatment of DMD. Other commercially available oral corticosteroids include methylprednisolone and prednisolone, and all are 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.

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 if switching from one corticosteroid to another improves tolerability. 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 than DMD, including a variety of inflammatory conditions.

Clinical Efficacy
There is moderate certainty that corticosteroids are safe and effective in the management of patients with 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). [2] The systematic review included the two pivotal trials used by the FDA for the approval of deflazacort (Emflaza). [3,4]
  - 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). [3]
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). [4]
- 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). [5]

- Two recent longer-term observational trials support the efficacy of corticosteroids for long term use in DMD. [6,7] 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. [8,9] 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) may be considered medically necessary for patients who have failed treatment with other corticosteroids. 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) thromboctopenic 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]

The AAN guidelines indicate some potential for superior tolerability with deflazacort (Emflaza) as compared to prednisone. [8] 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. [5] 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. [6] 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. [7]
- 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 gain, increased appetite, upper respiratory tract infection, cough, pollakiuria, hirsutism, central obesity, and nasopharyngitis. [1]. 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. [1]. Specific adverse reactions resulting from use of deflazacort (Emflaza) are serious skin rashes (toxic epidermal necrolysis) reported within 8 weeks of starting treatment. [1]

References


Billing Coding/Physician Documentation Information

Emflaza is considered a pharmacy benefit.

Additional Policy Key Words

N/A

Policy Implementation/Update Information

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<th>Date</th>
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