Emflaza (deflazacort) Prior Authorization with Quantity Limit Program Summary

FDA APPROVED INDICATIONS AND DOSAGE[1]

Agents	FDA Labeled Indications	Dosage and Administration
Emflaza (delflazacort)	• Treatment of Duchenne muscular dystrophy (DMD) in patients 5 years of age and older	0.9 mg/kg/day orally

CLINICAL RATIONALE

Duchenne muscular dystrophy (DMD) is one of nine primary types (>30 forms known) of muscular dystrophy.[3, 5] Prevalence in the United States is not exactly known, but is estimated to be approximately 1.0-1.8 per 10,000 males age 5-24 years old.[4] It is an X-linked recessive inherited genetic disorder primarily affecting boys, but in rare cases it can affect girls. Specifically, the dystrophin gene is affected. Dystrophin is located on the cytoplasmic face of the plasma membrane of muscle fibers and provides mechanical reinforcement to the sarcolemma and stabilizes the glycoprotein complex. This helps stave off degradation and digestion of the glycoprotein complex by proteases. Mutations in the dystrophin gene, and subsequent lack of dystrophin in the glycoprotein complex, result in a rapidly progressing disease involving muscle degeneration and weakness. Symptom onset is in early childhood and many are using a wheelchair in some capacity by 7-12 years of age. Beyond muscle weakness, some common symptoms are pseudohypertrophy of the calf muscles, cardiomyopathy, and poor respiratory function.[2] Currently, there is no cure for DMD and therapies are supportive in nature. Physical therapy, occupational therapy, respiratory care, speech therapy, braces/wheelchairs/contractures and glucocorticoid therapy are among the many common therapies.

Guidelines

The American Academy of Neurology (AAN) indicates that glucocorticoids are the only medication currently available that slows 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. Initial randomized controlled trials in patients treated with prednisone for up to 6 months showed an improvement in muscle strength, with 0·75 mg/kg daily having the most favorable profile. 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.[6]

In patients who have used glucocorticoids while ambulatory, many experts continue medication after loss of ambulation, with the goal of preserving upper limb strength, reducing progression of scoliosis, and delaying decline in respiratory and cardiac function. Indications for initiation of glucocorticoids in non-ambulatory patients are more relative than absolute. The effectiveness of glucocorticoid treatment in preventing scoliosis or in stabilizing cardiac or respiratory function in this setting is not known; this issue thus warrants further study. However, limited data from trials suggest short-term stabilization of pulmonary function in the early non-ambulatory patient. 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 cost, formulation, and perceived side-effect profiles. Prednisone is inexpensive and available in a tablet and liquid formulation. Deflazacort is more expensive and available in fewer tablet sizes.[6]

The updated AAN practice guidelines concluded that prednisone and deflazacort are possibly equally effective for improving motor function in patients with DMD (2 Class III studies). There is insufficient evidence to directly compare the effectiveness of prednisone vs deflazacort in cardiac function in patients with DMD (1 Class III study of a combined cohort). Additionally, prednisone is possibly associated with greater weight gain in the first 12 months of treatment, with no significant difference in weight gain with longer-term use compared with deflazacort (2 Class III studies). Deflazacort is possibly associated with an increased risk of cataracts compared with prednisone, although most are not vision-impairing (2 Class III studies).[7] The AAN states that deflazacort could be offered as an intervention for patients with DMD to 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). There is insufficient evidence to establish a difference in effect on cardiac function (Level U).[7]

Efficacy[1]
Emflaza (deflazacort) is a corticosteroid prodrug whose active metabolite acts through the glucocorticoid receptor to exert anti-inflammatory and immunosuppressive effects. The precise mechanism by which deflazacort exerts its therapeutic effects in patients with Duchenne muscular dystrophy (DMD) is unknown.

The effectiveness of Emflaza for the treatment of DMD was established in one multicenter, randomized, double-blind, placebo-controlled, 52-week study. 196 male patients between the ages of 5 and 15 years old with documented mutation of the dystrophin gene, onset of weakness before 5 years of age, and serum creatinine kinase activity at least 10 times the upper limit of normal at some stage in their illness were enrolled. Patients were randomized to receive Emflaza (0.9 or 1.2 mg/kg/day), an active comparator, or placebo. After 12 weeks, placebo patients were re-randomized to receive either Emflaza or the active comparator.

Efficacy was evaluated by assessing the change between Baseline and Week 12 in average strength of 18 muscle groups. The change in average muscle strength score between Baseline and Week 12 was significantly greater for the deflazacort 0.9 mg/kg/day dose group than for the placebo group. (p-value 0.017).

Safety[1]
Emflaza is contraindicated in patients with known hypersensitivity to deflazacort or to any of the inactive ingredients. Instances of hypersensitivity, including anaphylaxis, have occurred in patients receiving corticosteroid therapy.

Dosing: The recommended oral dosage of Emflaza is approximately 0.9 mg/kg/day once daily. If tablets are used, round up to the nearest possible dose. Any combination of the four Emflaza tablet strengths can be used to achieve this dose. If the oral suspension is used, round up to the nearest tenth of a milliliter (mL).

REFERENCES

1. Emflaza prescribing information. Marathon Pharmaceuticals. February 2017.
2. Darras BT. UpToDate Duchenne and Becker muscular dystrophy: Glucocorticoid and disease-modifying treatment. Last updated March 2018.

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4. Centers for Disease Control and Prevention (CDC). Muscular Dystrophy. http://www.cdc.gov/ncbddd/musculardystrophy/data.html; http://www.cdc.gov/ncbddd/musculardystrophy/features/key-findings-population-duchenne.html. Accessed July 2018.
5. National Institutes of Health (NIH). "What are the types of muscular dystrophy?" https://www.nichd.nih.gov/health/topics/musculardys/conditioninfo/pages/types.aspx. Accessed July 2018.
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7. Gloss MD, David, et al. Practice guideline update summary: Corticosteroid treatment of Duchenne muscular dystrophy. Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology February 2, 2016 vol.86 no. 5 465-472. doi: http://dx.doi.org/10.1212/WNL.0000000000002337. http://www.neurology.org/content/86/5/465.full.

Emflaza (deflazacort) Prior Authorization with Quantity Limit

OBJECTIVE
The intent of the prior authorization (PA) requirement for Emflaza is to encourage appropriate selection of patients for treatment according to product labeling and/or clinical studies and/or guidelines and according to dosing recommended in product labeling.

TARGET AGENT(S)
Emflaza® (deflazacort)

Brand (generic)	GPI	Multisource Code	Quantity Limit
Emflaza (deflazacort)			
6 mg tablet	22100017000340	M, N, O, or Y	2 tablets/day
18 mg tablet	22100017000350	M, N, O, or Y	1 tablet/day
30 mg tablet	22100017000360	M, N, O, or Y	N/A
36 mg tablet	22100017000365	M, N, O, or Y	N/A
22.75 mg/mL oral suspension	22100017001830	M, N, O, or Y	N/A

INITIAL PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
The requested agent will be approved when ALL of the following are met:

1. The patient has a diagnosis of Duchenne Muscular Dystrophy (prescriber must provide genetic test to confirm diagnosis)
   AND
2. The patient is at least five years old
   AND
3. ONE of the following:
   a. The patient has tried and failed a generic prednisone (or prednisolone) for at least 6 months
      OR
   b. The patient has a documented adverse reaction, intolerance, or contraindication to therapy with generic prednisone that is not expected to occur with the requested agent (prescriber must submit documentation)
   AND
4. The patient does NOT have any FDA labeled contraindications to therapy with the requested agent
   AND
5. The prescriber has provided the patient's weight
   AND
6. The dose requested is within FDA labeled dosing based on the patient's weight (i.e., 0.9 mg/kg/day)
   AND
7. The requested quantity (dose) is less than or equal to the program quantity limit (if applicable)

Length of Approval: 12 months

Renewal Evaluation
The requested agent will be approved when ALL of the following are met:

1. The patient has been previously approved for therapy with the requested agent through Prime Therapeutics PA process
   AND
2. The patient has had improvement, stabilization of the patient's disease, or clinical benefit [(e.g., improve strength and timed motor function, improve pulmonary function, reduce the need for scoliosis surgery)]
   AND
3. The patient does NOT have any FDA labeled contraindications to therapy with the requested agent
   AND
4. The prescriber has provided the patient's weight
   AND
5. The dose requested is within FDA labeled dosing based on the patient's weight (i.e., 0.9 mg/kg/day)
   AND
6. The requested quantity (dose) is less than or equal to the program quantity limit (if applicable)

Length of Approval: 12 months

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