

CENTENE PHARMACY AND THERAPEUTICS  
DRUG REVIEW  
2Q17 April – May

**BRAND NAME**

Emflaza<sup>™</sup>

**GENERIC NAME**

Deflazacort

**MANUFACTURER**

Marathon Pharmaceuticals, LLC

**DATE OF APPROVAL**

February 9, 2017

**PRODUCT LAUNCH DATE**

Anticipated availability in early 2017

**REVIEW TYPE**

Review type 1 (RT1): New Drug Review  
*Full review of new chemical or biologic agents*

Review type 2 (RT2): New Indication Review  
*Abbreviated review of new dosage forms of existing agents that are approved for a new indication or use*

Review type 3 (RT3): Expedited CMS Protected Class Drug Review  
*Expedited abbreviated review of Centers for Medicare & Medicaid Services protected class drugs (anticonvulsants, antidepressants, antineoplastic, antipsychotics, antiretrovirals, and immunosuppressants)*

**FDA APPROVED INDICATION(S)**

Emflaza is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients 5 years of age and older.

**OFF-LABEL USES**

Not applicable

**CLINICAL EFFICACY<sup>1,2</sup>**

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 US and Canada. The study population consisted of 196 male pediatric patients 5 to 15 years of age with

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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 (ULN) at some stage in their illness. Patients were randomized to therapy with 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 placebo (n=50). A comparison to placebo was made after 12 weeks of treatment. After 12 weeks, placebo patients were re-randomized to 1 of the 3 active treatment groups; all patients continued treatment for an additional 40 weeks. Baseline characteristics were comparable between the treatment arms.

The primary efficacy endpoint was the average change in muscle strength from baseline to week 12 compared with placebo. Individual muscle strength was graded using a modified Medical Research Council (MRC) 11-point scale, with higher scores representing greater strength. The primary efficacy analysis demonstrated a significant least squares mean difference in favor of deflazacort 0.9 mg/kg/day (0.25 vs -0.1, p=0.017, 95% CI 0.04–0.46), deflazacort 1.2 mg/kg/day (0.36 vs -0.1, p=0.0003, 95% CI 0.14–0.57), and prednisone 0.75 mg/kg/day (0.37 vs -0.1, p=0.0002, 95% CI 0.15–0.59) compared with placebo in muscle strength at 12 weeks.

Secondary efficacy endpoints included change in average muscle strength from week 12 to week 52 and pulmonary function testing (i.e., forced vital capacity [FVC] and maximum voluntary ventilation). Additional endpoints included timed functional testing: standing from lying position; climbing 4 stairs; running/walking 30 feet; and propelling a wheelchair 30 feet. There was a significant improvement in average muscle strength score from week 12 to week 52 in the deflazacort 0.9 mg/kg/d group compared with the prednisone-treated group (LS mean 0.29, p= 0.044, 95% CI 0.08–0.49). The deflazacort 1.2 mg/kg/d group had numerical improvement compared to prednisone treated participants from week 12 to week 52 but it did not reach significance (LS mean 0.16, p 5 0.18, 95% CI 20.06 to 0.37). From week 12 to week 52, both deflazacort groups demonstrated greater numerical improvements in time from supine to stand, time to climb 4 stairs, and time to run or walk 30 feet compared with the prednisone-treated participants, but these did not reach significance. Pulmonary function assessments showed a significantly greater benefit with deflazacort 1.2 mg/kg/d over prednisone for the change in FVC from week 12 to week 52. No other differences between treatment groups were observed in assessments of pulmonary function.

Compared with the deflazacort 0.9 mg/kg/day group, the deflazacort 1.2 mg/kg/day group demonstrated a small additional benefit compared to placebo at Week 12, but had a greater incidence of adverse reactions. Therefore, use of a 1.2 mg/kg/day dosage of Emflaza is not recommended.

Although not a pre-specified statistical analysis, compared with placebo, the deflazacort 0.9 mg/kg/day dose group demonstrated at Week 52 the persistence of the treatment effect observed at Week 12 and the small advantage of the 1.2 mg/kg/day dose that was observed at Week 12 was no longer present. Also not statistically controlled for multiple comparisons, results on several timed measures of patient function (i.e., time to stand from supine, time to climb 4 stairs,

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and time to walk or run 30 feet) numerically favored deflazacort 0.9 mg/kg/day at Week 12, in comparison with placebo.

An additional randomized, double-blind, placebo-controlled, 104-week clinical trial evaluated deflazacort in comparison to placebo. The study population consisted of 29 male children 6 to 12 years of age with a DMD diagnosis confirmed by the documented presence of abnormal dystrophin or a confirmed mutation of the dystrophin gene. The results of the analysis of the primary endpoint of average muscle strength scores (graded on a 0-5 scale) at 2 years were not statistically significant, possibly because of a limited number of patients remaining in the placebo arm (subjects were discontinued from the trial when they lost ambulation). Although not statistically controlled for multiple comparisons, average muscle strength scores at Months 6 and 12, as well as the average time to loss of ambulation, numerically favored deflazacort in comparison with placebo.

**CONTRAINDICATIONS**

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.

**BLACK BOX WARNINGS**

Not applicable

**DRUG INTERACTIONS**CYP3A4 Inhibitors and Inducers

- Moderate or strong CYP3A4 inhibitors: Give one third the recommended dosage of Emflaza when moderate or strong CYP3A4 inhibitors (e.g., clarithromycin, fluconazole, diltiazem, verapamil, grapefruit juice) are used concomitantly with Emflaza.
- Moderate or strong CYP3A4 inducers: Avoid concomitant use of strong (e.g., efavirenz) or moderate (e.g., carbamazepine, phenytoin) CYP3A4 inducers with Emflaza, as they may reduce efficacy.

Neuromuscular Blockers

- Patients receiving corticosteroids, including Emflaza, and concomitant therapy with neuromuscular blocking drugs (e.g., pancuronium) may be at increased risk of developing an acute myopathy.

**ADVERSE REACTIONS**

The most common adverse reactions ( $\geq 10\%$  for Emflaza and greater than placebo) are Cushingoid appearance, increased weight, increased appetite, upper respiratory tract infection, cough, pollakiuria, hirsutism, central obesity, and nasopharyngitis.

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**DOSAGE AND ADMINISTRATION**

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). Emflaza tablets and oral suspension can be taken with or without food.

Dosage of Emflaza must be decreased gradually if the drug has been administered for more than a few days.

**PRODUCT AVAILABILITY**

Tablets: 6 mg, 18 mg, 30 mg, and 36 mg

Oral suspension: 22.75 mg/mL

**THERAPEUTIC ALTERNATIVES**

| DRUG NAME                     | USAGE REGIMEN<br>(route of admin/frequency of use)  | COMMENTS  |
|-------------------------------|---|---|
| <b>Prednisone (Deltasone)</b> | 0.75 mg/kg/day PO (preferred)<br><br><u>Alternative dosing regimens</u> <ul style="list-style-type: none"> <li>• 0.3 mg/kg/day PO (<i>lesser efficacy and fewer adverse events</i>)</li> <li>• 10 mg/kg/weekend PO</li> </ul> | Off-label indication; however, prednisone is recommended by the American Academy of Neurology guideline on corticosteroid treatment of DMD, which was also endorsed by the American Academy of Pediatrics; by the American Association of Neuromuscular & Electrodiagnostic Medicine; and by the Child Neurology Society. |

**Boldface indicates generic availability**

| <b>Utilization Management Recommendation</b>  |
|---|
| <ul style="list-style-type: none"> <li>• There is significant potential for inappropriate use and utilization management should be considered for the following reason(s):               <ul style="list-style-type: none"> <li>i) To prevent inappropriate use of medications that have a significant potential for use that may lead to inferior or unpredictable outcomes.                   <ul style="list-style-type: none"> <li>(1) Emflaza is an oral corticosteroid and can potentially be used off-label in conditions where corticosteroids are indicated;</li> <li>(2) To ensure that Emflaza is used only in the treatment of Duchenne muscular dystrophy.</li> </ul> </li> <li>ii) Recommended utilization management tool(s): (check all that apply)                   <ul style="list-style-type: none"> <li>(1) <input checked="" type="checkbox"/> Prior authorization</li> </ul> </li> </ul> </li> </ul> |

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|  |                              |                             |
|--|------------------------------|-----------------------------|
|  | (2) <input type="checkbox"/> | Quantity limits             |
|  | (3) <input type="checkbox"/> | Provider newsletter         |
|  | (4) <input type="checkbox"/> | Hard block (plan exclusion) |
|  | (5) <input type="checkbox"/> | Messaging                   |
|  | (6) <input type="checkbox"/> | Electronic step therapy     |
|  | (7) <input type="checkbox"/> | Clinical Program            |
| Product Comparison   |                              |                             |
| <ul style="list-style-type: none"> <li>• CPAC score: 53 vs. Prednisone – Equal therapeutic outcomes anticipated</li> <li>• Equal therapeutic outcomes are anticipated for Emflaza and prednisone; therefore, it would be appropriate to provide equal access to both or to require a trial of one before the other.</li> </ul> |                              |                             |

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**REFERENCES**

1. Emflaza Prescribing Information. Northbrook, IL: Marathon Pharmaceuticals, LLC; February 2017; Available at: <https://emflaza.com/>. Accessed February 21, 2017.
2. Griggs RC, Miller JP, Greenberg CR, et al. Efficacy and safety of deflazacort vs prednisone and placebo for Duchenne muscular dystrophy. *Neurology*. 2016;87(20):2123-2131. doi:10.1212/WNL.0000000000003217.
3. 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;86(5):465-472. doi:10.1212/WNL.0000000000002337.