

**Brand Name:** Emflaza

**Generic Name:** Deflazacort

**Manufacturer:** Marathon Pharmaceuticals, LLC

**Drug Class:** Corticosteroid

**Uses<sup>1,5</sup>:**

- **Labeled:** Duchenne muscular dystrophy
- **Unlabeled:** None

**Mechanism of Action<sup>1</sup>:** Acts through the glucocorticoid receptor to exert anti-inflammatory and immunosuppressive effects. Precise mechanism is unknown.

**Pharmacokinetics<sup>1,2,3,5</sup>:**

- Absorption

<b>T<sub>max</sub></b>	1 hour
<b>V<sub>d</sub></b>	Not reported
<b>T<sub>1/2</sub></b>	12 hours
<b>Clearance</b>	Not reported
<b>Protein binding</b>	40%
<b>Bioavailability</b>	Similar to oral suspension

- o When taken with food, T<sub>max</sub> delayed by 1 hour and C<sub>max</sub> reduced by 30%
- Metabolism
  - o Metabolized rapidly by esterases
  - o Major CYP3A4 substrate
- Excretion
  - o Renal excretion: 18% changed, 68% unchanged

**Safety/Efficacy<sup>6,7,8</sup>:**

Bonifati MD, Ruzza G, Bonometto P, Berardinelli A, Gorni K, Orcesi S, et al. A multicenter, double-blind, randomized trial of deflazacort versus prednisone in Duchenne muscular dystrophy. *Muscle Nerve*. 2000; 23:1344-1347.

- Study design:
  - o Multi center, double-blind, randomized, controlled trial
- Description of study:
  - o Methods
    - Eighteen Duchenne Muscular Dystrophy patients were randomized to treatment with deflazacort or prednisone. The authors also used natural history controls to compare with the active treatment groups. Inclusion criteria were the diagnosis of DMD confirmed by dystrophin immunohistochemistry, age over 5 years, preserved ability to ambulate independently, and no previous steroid therapy. Each patient was evaluated for muscle strength by the medical Research Counsel (MRC) scale in

four muscles and functionality that looked at gait, rising from a chair and from the floor, and climbing steps. Both measures were evaluated at baseline and at 3, 6, 9, and 12 months.

- Results
  - After the 12 month study period, there was no significant difference found between deflazacort and prednisone in either MRC score or functionality score. One patient dropped out of the study during follow-up due to the loss of independent ambulation. There was a significantly larger mean increase in weight in the prednisone group (21.3%) compared to the deflazacort group (9%) at 12 months ( $P < 0.05$ ). There were no significant changes in laboratory parameters between the two groups.
- Limitations:
  - Small sample size
  - No power reported for the study
- Conclusion:
  - There is no difference in efficacy when comparing deflazacort and prednisone for the treatment of DMD. The authors acknowledge that there could have been a possibility of type II error due to small sample size, however no power for the study was published. In addition, it appears as though there may be a side effect profile advantage to using deflazacort, especially pertaining to weight gain.

Ferraris JR, Pasqualini T, Legal S, et al. Effect of deflazacort versus methylprednisone on growth, body composition, lipid profile, and bone mass after renal transplantation. *Pediatr Nephrol.* 2000; 14:682-88.

- Study design:
  - Prospective, open-label, randomized, parallel group, multicenter study
- Description of study:
  - Methods:
    - Twenty-seven patients that had previously received a kidney transplant (approximately 2 years prior) were randomized to be switched to deflazacort or remain on methylprednisone. Inclusion criteria were that patients were prepubertal, at least 6 months since the kidney transplant procedure, at least 6 months of stable kidney function, and not on lipid-lowering therapy. Pubertal status, weight, and height were evaluated at 6-month intervals. Laboratory studies were also performed at 6-month intervals. Twenty-four-hour urine samples were collected at baseline and after 12 months in order to analyze calcium and creatinine levels. Bone mass was assessed at baseline and at 12 months.
  - Results
    - For the evaluation of renal function, there was a significant decrease in creatinine clearance from baseline in the methylprednisone group (66.3 ml/min at baseline compared to 58.3 mL/min at 1 year,  $P < 0.025$ ), but not in the deflazacort group. In addition, there was one acute rejection episode in the methylprednisone group compared to none in the deflazacort group. There was a significant difference in the

intergroup height velocity at the end of one year (standard deviation score of -3.3 for the methylprednisolone vs. -0.5 for the deflazacort group;  $P < 0.0005$ ). Total body mass increased significantly in both groups, but increased more in patients on methylprednisone (3.5 kg) compared to deflazacort (1.6 kg) ( $P < 0.05$ ). The methylprednisolone group had an increase in total cholesterol of 9.9% ( $P < 0.05$ ) and LDL-cholesterol of 12.5% ( $P < 0.025$ ), whereas the deflazacort group had no change for these values. However, the HDL-cholesterol levels in the deflazacort actually increased by 21% ( $P < 0.005$ ), while there was no change in the methylprednisolone group. Bone mineral density of both lumbar spine and total skeleton were unchanged in the deflazacort group, but significantly declined in the methylprednisone group.

- Limitations:

- Small sample size
- No power reported in the study
- Evaluating kidney function based off of creatinine clearance may not be appropriate for determining long-term effects on the kidney
- Study was carried out only in Argentina, may not have high external validity
- The follow-up period was only one year and these patients would likely be on these medications much longer than one year

- Conclusion:

- From the results of this study it appears that substituting deflazacort for maintenance methylprednisone therapy in pediatric patients who have received a kidney transplant results in an improved side effect profile, specifically regarding linear growth, bone loss, and fat accumulation. However, the study has several limitations that cannot be overlooked. First, this study has a small sample size, therefore the results may not be indicative of the entire population. Also, the authors claim that kidney function was better in the deflazacort group by looking at the results for creatinine clearance. Creatinine clearance can be a relatively variable lab value, so determining kidney function off of one reading at baseline and another reading at 1 year is probably not the best way to determine kidney function. Finally, a one year follow-up period may not be enough to determine long-term safety and efficacy of these two medications. Further studies should be carried out to determine the long term effects of deflazacort use.

Balaban B, Matthews DJ, Clayton GH, Carry T. Corticosteroid treatment and functional improvement in Duchenne muscular dystrophy: Long-term effect. *Am J Phys Med Rehabil* 2005;84:843–850.

- Study design:

- Retrospective cohort study

- Description of study:

- Methods:

- Forty-nine male children between the ages of 7 and 15 years were observed over a 7 year period. Eighteen were treated with prednisone, 12 with deflazacort, and 19 had no drug treatment and served as the control. All boys treated with steroids received medication for greater than 2 years before losing their ambulation. Lower and upper limb motor functions, pulmonary function, prevalence of surgery for scoliosis, and side effects were compared. Lower limb functionality was assessed by measurement of time needed to walk or run 30 feet, time to get up from the floor, time to climb four standard-size steps, and time to stand from a sitting position. Upper limb functionality was assessed by grip and pinch strength and maximum hand-held weight that could be lifted overhead. Pulmonary function was determined by a hand-held spirometer. Side effects were monitored by a patient questionnaire and by routine urine and blood examination. Radiographic evaluation of the spine was evaluated once per year.
- Results:
  - The number of boys that were able to do all of the motor function tests was significantly higher in the steroid groups compared to the non-treated boys ( $P < 0.05$ ). There was no significant difference between the two steroid groups ( $P > 0.05$ ). Back surgery occurred in 52.6% ( $n=10$ ) of the patients in the control group, 11.1% ( $n=2$ ) of patients in the prednisone group, and none of the patients in the deflazacort group. This was a statistically significant difference when comparing the steroid groups vs. the non-treated group ( $P < 0.05$ ). Although each group had a drop in FVC, there was no difference between the three groups for intergroup comparison ( $P > 0.05$ ). The prednisone group had a more profound weight gain effect compared to the deflazacort and control group. Three boys in the prednisone group discontinued their medication due to excessive weight gain compared to none in the other two groups. The deflazacort treatment of three boys was tapered due to hypertension, behavioral changes, and vertebral fracture.
- Limitations:
  - Study design was not ideal
  - No primary outcome specifically designated
  - Small sample size
  - The patient's parents were offered the option of steroid or not. The families also had to pay for the cost of the medication, which led them to choose against the steroid medication.
- Conclusion:
  - This study provides a base for further research to be completed on the efficacy and safety of deflazacort compared to other steroid medications for the use in patients with Duchenne Muscular Dystrophy. Although the study did show promising results for the safety and efficacy of deflazacort, the study design was poor, the sample size was small, and there was no clear primary outcome of the study. Further randomized, controlled trials are needed to prove the efficacy and safety of this medication.

**Contraindications<sup>1, 2, 3</sup>:** Contraindicated in patients who have a known hypersensitivity to deflazacort. Avoid live vaccine administration while using this medication.

**Precautions<sup>1</sup>:**

- Monitor for signs of infection
- Prolonged administration of corticosteroids can result in hypothalamic-pituitary-adrenal suppression
- Avoid in patients with Cushing's syndrome
- Use caution in diabetic patients
- Use caution in patients with thyroid disorders
- Use caution in patients with pheochromocytoma
- Use caution in patients with CHF, HTN, or renal disease
- Use caution in patients with psychosis or emotional instability
- Use caution in patients with glaucoma

**Adverse effects<sup>1, 2, 3, 5</sup>:**

- Occurring in >10% of patients:
  - **Dermatologic**
    - Hirsutism (10-35%)
  - **Endocrine**
    - Central obesity (10-35%)
    - Cushingoid facies (33-60%)
    - Weight gain (20-28%)
  - **Gastrointestinal**
    - Increased appetite (14%)
  - **Renal**
    - Increased frequency of urination (12-15%)
  - **Respiratory**
    - Cough (12%)
    - Nasopharyngitis (10%)
    - Upper respiratory infection (12%)
- Occurring in 1-10% of patients:
  - **Psychological**
    - Irritability (8-10%)
    - Abnormal behavior (9%)
    - Psychomotor hyperactivity (6%)
  - **Dermatologic**
    - Toxic epidermal necrosis
    - Rash (7%)
    - Skin striae (6%)
  - **Hematologic**
    - Epistaxis (6%)
    - Contusion (6%)
  - **Endocrine**
    - Cushing's syndrome
    - Hyperglycemia
    - HPA axis dysfunction
  - **Immunologic**

- Anaphylaxis

#### **Drug Interactions<sup>2, 3, 4</sup>:**

- Bupropion: may result in increased risk of seizure
- NSAIDs: may result in increased risk of gastrointestinal bleeding
- Aldesleukin: may result in decreased antitumor effectiveness of aldesleukin
- Bemiparin: may result in increased risk of bleeding
- Nadroparin: may result in increased risk of bleeding
- Antacids: may result in decreased effectiveness of deflazacort
- Fluoroquinolones: may result in increased risk of tendon rupture
- CYP3A4 strong/moderate inducers: decreased serum concentrations of deflazacort
  - Aminoglutethimide, bexarotene, bosentan, carbamazepine, dexamethasone, efavirenz, fosphenytoin, griseofulvin, modafinil, nafcillin, nevirapine, oxcarbazepine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentine, St. John's wort
- CYP3A4 strong/moderate inhibitors: increased serum concentrations of deflazacort
  - Amiodarone, amprenavir, aprepitant, atazanavir, chloramphenicol, clarithromycin, conivaptan, cyclosporine, dasatanib, delavirdine, diltiazem, erythromycin, fluconazole, fluoxetine, fluvoxamine, fosamprenavir, grapefruit juice, imatinib, indinavir, isoniazid, itraconazole, ketoconazole, lapatinib, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, quinupristin, saquinavir, tamoxifen, telithromycin, troleandomycin, verapamil, voriconazole

#### **Dosing/Administration<sup>1, 2, 3, 5</sup>:**

- Usual dose: 0.9 mg/kg orally once daily; round up to next possible dose for tablets; round up to nearest tenth of a mL for oral suspension
- Pediatric dose (5 years and older): 0.9 mg/kg orally once daily; round up to next possible dose for tablets; round up to nearest tenth of a mL for oral suspension
- No dosage adjustment for renal impairment
- No dosage adjustment for hepatic impairment

#### **Use in special circumstances<sup>1, 2, 3, 5</sup>:**

- No adequate trials for use in pregnancy. Use of corticosteroids in pregnancy may result in complications such as orofacial clefts, intrauterine growth restriction, and decreased birth weight
- Corticosteroids distribute into breast milk and may cause adverse effects to the infant
- Give one-third of the usual oral dose when taking with moderate or strong CYP3A4 inhibitors
- Avoid use when patients are taking moderate or strong CYP3A4 inducers

#### **Conclusion:**

Deflazacort appears to be effective for the treatment of Duchenne Muscular Dystrophy in the pediatric population. There are a limited amount of studies that are mostly dated, but the available data suggests that deflazacort is efficaciously comparable to other available steroid medications, such as prednisone. Where deflazacort may show an advantage to other steroid medications is in its side effect profile. The available data suggests that deflazacort may cause less steroid-like side effects compared to other

widely used steroid medications. However, the studies are mostly of small sample size and more studies should be carried out to reinforce this notion.

#### References:

1. Deflazacort. Clinical Pharmacology [Internet database]. Elsevier, Inc., 2017. Available at <http://www.clinicalpharmacology.com>. Accessed: March 28, 2017.
2. Deflazacort. In: DRUGDEX System [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed March 28, 2017.
3. Deflazacort. Facts & Comparisons Online [Internet database]. Wolters Kluwer. Available at: <http://online.factsandcomparisons.com>. Accessed March 28, 2017.
4. Horn JR, Hansten PD. Get to know an enzyme: CYP3A4. Pharmacy Times. September, 2008. Available at: <http://www.pharmacytimes.com/publications/issue/2008/2008-09/2008-09-8687>. Accessed September 27, 2016.
5. Emflaza [package insert]. Northbrook, IL: Marathon Pharmaceuticals, LLC; 2017.
6. Bonifati MD, Ruzza G, Bonometto P, Berardinelli A, Gorni K, Orcesi S, et al. A multicenter, double-blind, randomized trial of deflazacort versus prednisone in Duchenne muscular dystrophy. *Muscle Nerve*. 2000; 23:1344-1347.
7. Ferraris JR, Pasqualini T, Legal S, et al. Effect of deflazacort versus methylprednisone on growth, body composition, lipid profile, and bone mass after renal transplantation. *Pediatr Nephrol*. 2000; 14:682-88.
8. Balaban B, Matthews DJ, Clayton GH, Carry T. Corticosteroid treatment and functional improvement in Duchenne muscular dystrophy: Long-term effect. *Am J Phys Med Rehabil* 2005;84:843–850.