Washington State Health Care Authority

# Deflazacort Clinical Policy

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Washington State Health Care Authority

# Overview

- Duchenne Muscular Dystrophy Background and Epidemiology
- Evidence on Safety and Efficacy of Deflazacort
- Clinical Policy

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# Duchenne Muscular Dystrophy Background and Epidemiology

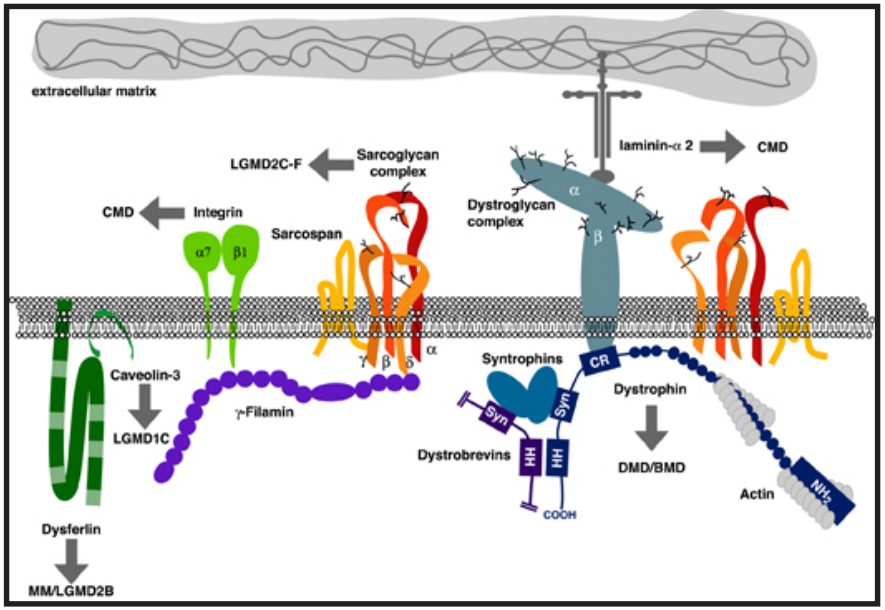
# Duchenne Muscular Dystrophy (DMD)

- Duchenne muscular dystrophy (DMD) is an X-linked genetic disease affecting the dystrophin gene.

- Dystrophin is a protein that interfaces between the plasma cell membrane of muscle fibers and extracellular matrix[1].

  - Dystrophin is necessary for normal muscle function, protecting the glycoprotein complex at the membrane.

  - Loss of dystrophin results in degeneration of muscle fibers, resulting in muscle weakness, the primary symptom of DMD.




From UpToDate[1]. The dystrophin associated protein complex. Courtesy of Dr. K. O'Brien and Dr. L. Kunkel, Children's Hospital, Boston, MA.

# Duchenne Muscular Dystrophy (DMD)

- DMD typically manifests as muscle weakness in males at 2 to 3 years of age[1]. Diagnosis of DMD often occurs around age 5[2].
  - Genetic tests or muscle biopsy are required to confirm diagnosis of DMD compared to other dystrophinopathies (such as Becker muscular dystrophy [BMD])[1,2].
- Muscle weakness begins in the distal limb muscles, resulting in difficulty running, jumping, and even walking[1].
  - About 82% of patients with DMD are restricted to wheelchairs between 10 through 14 years of age[2].
- Cardiomyopathy, caused by fibrosis of the left ventricular wall, can lead to heart failure and arrhythmias in the patient's teenage years[1]. Other significant medical complications from DMD are respiratory, bone fractures, and mental health.
- The most common cause of death is acute respiratory failure (due to scoliosis and progressive muscle weakness)[1]. The majority of deaths occur in the 20s.

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# DMD Epidemiology

- A population-based survey in 4 US states estimates the prevalence of DMD and BMD to be 1 in 7,250 males ages 5 to 24[2]. It was estimated that, out of 2.37 million males ages 5 to 24 in 4 US states, there were 349 with DMD or BMD[3].
  - Other prevalence studies conducted in the US, Canada, Northern England, and Wales found similar population estimates[1].
- DMD has higher prevalence among Hispanics and non-Hispanic whites than among non-Hispanic blacks[2].
- The prevalence of DMD in Washington Medicaid FFS is estimated to be 100. The incidence of new DMD cases by birth is estimated to be 6.

# DMD Standard of Care

- Glucocorticoids can help improve motor function, pulmonary function, and reducing the risk of scoliosis in patients with DMD[1].
  - Treatment with steroids typically begins around 7 years of age[2].
  - Approximately 57% to 69% of patients with DMD and BMD are treated with steroids[2]. Prednisone is the most commonly used steroid (between 64% to 78%)[2].
- Cardiac, pulmonary, orthopedic, mental health, nutritional, growth, weight, and pain conditions are all commonly associated with DMD as well[1].

# Evidence on Safety and Efficacy of Deflazacort

# Deflazacort vs. prednisone

- Deflazacort was studied against prednisone for the treatment of DMD in 4 randomized control trials
  - All four studies were rated by GRADE system to have very low quality of evidence on outcomes of muscle strength, motor outcomes, weight gain, and cataracts.
  - The quality of evidence for comparative effectiveness outcomes were downgraded due to risk of bias, imprecision, and lack of applicability
- There is no comparative evidence for deflazacort and prednisone beyond 2 years of use for DMD.

# Deflazacort vs. prednisone

- Reitter (1995); Dubowitz (2000) published the results of a trial of deflazacort vs. prednisone in boys with DMD or BMD from 1995.
  - N = 100; study duration = 2 years
  - No statistically significant difference in muscle strength (Medical Research Council scale score) or motor outcomes
  - Prednisone group had more weight gain (no data) while deflazacort group developed more cataracts (36% vs. 3%), and 20% of enrollees did not complete the study (14 discontinued due to weight gain)
- Reitter (1995) published interim results from 67 boys in 1995 and only presented graphical data without reporting data by intervention group. Dubowitz (2000) presented the results of 100 boys at a conference workshop.

# Deflazacort vs. prednisone

- Brooke (1996); Griggs (2016) published the results of a trial of deflazacort vs. prednisone in boys with DMD or BMD from 1995.
  - N = 167; study duration = 3 months (primary) and 1 year (other outcomes)
  - Both deflazacort and prednisone were significantly more effective than placebo for both muscle strength and motor outcomes. No difference between active groups at 12 weeks or at 1 year.
  - Prednisone group had statistically significant weight gain at 1 year (mean difference of 5.05 kg vs 8.45 kg) while deflazacort group developed more cataracts (6.6% vs 4.4%).
- Results of the study were originally presented at the 75th American Academy of Neurology meeting (1996) but were published as part of the FDA clinical review (2016).

# Deflazacort vs. prednisone

- Bonifati (2000) published the results of a trial of deflazacort vs. prednisone in boys with DMD from 2000.
  - N = 18; study duration = 2 years
  - No statistically significant difference in muscle strength (Medical Research Council scale score) or motor outcomes (results were presented only graphically)
  - Prednisone group had more weight gain (mean difference from baseline: 8.7 kg vs. 4.6 kg) while deflazacort group developed more cataracts.
- No significant differences were found at 3, 6, or 9 months but found statistically significant improvement at 12 months with prednisone (the authors suggest that this is due to more severe patients dropping out of the study).

# Deflazacort vs. prednisone

- Karimzadeh (2012) published the results of a trial of deflazacort vs. prednisone in boys with DMD from 2012.
  - N = 34; study duration = 18 months
  - Deflazacort had a statistically significant difference in motor outcomes at 12 months but had no statistically significant difference at 18 months. Muscle strength was not evaluated.
  - Prednisone group had more weight gain at 12 months and 18 months.
- Study had significant loss to follow-up (17.6% deflazacort; 29.4% prednisone) and did not use intent-to-treat analysis. Authors did not report on randomization, blinding, or baseline characteristics.

# Systematic Reviews

- Three systematic reviews reviewed the evidence of deflazacort vs. prednisone for the treatment of DMD.
  - Each systematic review had different inclusion criteria and no systematic review included all 4 trials from the previous section.
- Two systematic reviews concluded that deflazacort and prednisone were similarly effective in muscle strength and motor outcomes and that deflazacort leads to less weight gain
- The third systematic review did not find enough evidence to make a conclusion on the effectiveness of motor outcomes and found very low quality evidence (high risk of bias) of prednisone causing more weight gain

# American Academy of Neurology Practice Guidelines on Corticosteroid Treatment of DMD (2016)

- The AAN Practice Guidelines on Corticosteroid Treatment of DMD was a good methodological quality guideline.
  - The only RCT included for this section was Bonifati et al., 2000
- The guidelines do not recommend one corticosteroid over the other and cited a low confidence in the quality of the comparative evidence
- Guidelines provide “B” level evidence [moderate value of benefit relative to risk and moderate confidence in evidence] for prednisone to improve strength and improve pulmonary function. All other outcomes for both prednisone and deflazacort are “C” level evidence [small value of benefit relavitve to risk and low confidence of evidence].

# Emflaza price?

- In February 2017, Marathon Pharmaceuticals announced a list price of Emflaza (deflazacort) to cost approximately $89,000 per patient per year. On March 16, PTC Therapeutics announced the purchase of Marathon Pharmaceuticals for $140 million. The new pricing for Emflaza has not been announced.
  - AWP for a single tablet was $294.00. New AWP has not been announced.
  - Deflazacort is administered as 0.9 mg/kg/day. The maximum tablet strength is 36 mg, so for patients above 88 lbs., deflazacort would require multiple tablets and increasing the cost even more
- Deflazacort was available from pharmacies in the United Kingdom for approximately $1000 per year.
- Prednisone is available at a MAC of $0.05 per 20 mg tablet. This translates to an approximate cost of $55 per patient per year.

# Conclusions

- Based on a review of the randomized clinical trials, systematic reviews and treatment guidelines:
  - there is very low quality evidence that there is no difference in efficacy between deflazacort and prednisone
  - there is very low quality evidence that prednisone is associated with more weight gain than deflazacort but clinical significance has not been studied
- Prednisone is the lower cost alternative based on current pricing information

# Deflazacort Clinical Policy

| For approval (initial and renewal): | |
|---|---|
| **Criteria** | **Rationale** |
| Prednisone will be the preferred corticosteroid for the treatment of DMD | Prednisone is the lower cost, equally effective alternative |
| Deflazacort will be reviewed on a case-by-case basis to determine medical necessity for the treatment of DMD | Very low quality of evidence on efficacy and safety. |
| Deflazacort will not be approved for off-label indications | Deflazacort for use in other disease states has not been evaluated by the FDA |

# Citations


1. Darras BT, Patterson MC, Firth HV, Dashe JF. Clinical features and diagnosis of Duchenne and Becker muscular dystrophy. UpToDate. Wolters Kluwer. Feb 10, 2017. https://www.uptodate.com/contents/treatment-of-duchenne-and-becker-muscular-dystrophy
2. Centers for Disease Control and Prevention (CDC). Musclar dystrophy. US Department of Health & Human Services. Jul 19, 2016. https://www.cdc.gov/ncbddd/musculardystrophy/data.html
3. Centers for Disease Control and Prevention (CDC). Musclar dystrophy. US Department of Health & Human Services. Apr 7, 2016. https://www.cdc.gov/ncbddd/musculardystrophy/facts.html
4. Carson S, Driver R, Harrod C. Emflaza (deflazacort) for children with Duchenne muscular dystrophy: Comparative effectiveness versus prednisone. Oregon Health & Science University Center for Evidence-based Policy: Portland, OR. Apr 2017.

# Questions?

Motion: “I move the Medicaid Fee-For-Service Program implement the limitations for deflazacort on slide 19 as recommended.”

Motion: Figueroa

2nd: Brown

Passed