New Drug Overview
Emflaza (deflazacort)

INTRODUCTION

- Duchenne muscular dystrophy (DMD) is an X-linked, recessive neuromuscular disorder caused by mutations of the dystrophin gene *(Food and Drug Administration [FDA] Summary Review 2017)*. These mutations disrupt the messenger ribonucleic acid (mRNA) reading frame, leading to the absence or near-absence of dystrophin protein in muscle cells *(FDA Summary Review 2017)*.
  - Dystrophin is thought to maintain the structural integrity of the muscle cell, cushioning it from the stress and strain of repeated contraction and relaxation *(FDA Summary Review 2017)*. Absence of dystrophin leads to muscle damage, with replacement by fibrotic and adipose tissue *(FDA Summary Review 2017)*.
  - The first symptoms of DMD typically emerge between 2 and 5 years of age and include frequent falls; difficulty with walking, standing, and balancing; difficulty in getting up from a lying or sitting position; trouble with running or jumping; waddling gait; and development of large calf muscles *(Emflaza Formulary Submission Dossier 2017, FDA Summary Review 2017, Muscular Dystrophy Association [MDA] Web site)*.
  - DMD patients progressively lose the ability to perform activities independently and often require use of a wheelchair by their early teens *(MDA Web site)*. With progressive degeneration of skeletal muscle (including breathing muscles) and cardiac muscle, patients typically succumb to the disease in their 20s or 30s; however, disease severity and life expectancy vary *(FDA Summary Review 2017, MDA Web site)*.
- DMD occurs in approximately 1 out of every 3600 to 6000 male births worldwide; female-manifesting carriers are rarer, but can present with a range of symptoms that vary in their severities *(FDA Medical Review 2017)*.
- Treatment for DMD has been largely supportive and utilizes corticosteroids such as prednisone, which are widely believed to delay the loss of ambulation (LoA) and respiratory decline by several years *(FDA Summary Review 2017, Gloss et al 2016, UpToDate 2017)*. Outside of the United States, the glucocorticoid, deflazacort, has been approved for various auto-immune disorders and hypersensitivity reactions for over 30 years; while both prednisone and deflazacort are considered standards of care for DMD, deflazacort has not previously been approved in any country for the treatment of DMD *(FDA Summary Review 2017)*.
- Following a priority review by the FDA, Emflaza (deflazacort) tablets and oral suspension were approved on February 9, 2017 for the treatment of DMD in patients ≥ 5 years of age *(FDA Web site)*. Deflazacort was additionally granted orphan drug and fast track designations.
- Deflazacort is a corticosteroid prodrug whose active metabolite (21-desDFZ) binds glucocorticoid receptors to exert immunosuppressive and anti-inflammatory effects. The precise mechanism by which deflazacort exerts its therapeutic effects in patients with DMD is unknown.
- Medispan Class: Corticosteroids; Glucocorticosteroids; Deflazacort

INDICATIONS

- Deflazacort is indicated for the treatment of DMD in patients 5 years of age and older *(Emflaza prescribing information 2017)*.

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The safety and efficacy of deflazacort were demonstrated in 2 pivotal, double-blind (DB), placebo-controlled (PC), multi-center, randomized controlled trials (RCTs) that were conducted in the 1980s and 1990s *(Angelini et al 1994, Emflaza Formulary Submission Dossier 2017, Griggs et al 2016)*.
- In Study 1 (MP-104-NM-001), 196 males diagnosed with DMD and between the ages of 5 and 15 years were randomized to receive treatment 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) for 12 weeks (Phase 1) *(Griggs et al 2016)*. Randomization was stratified according to ambulatory vs. non-ambulatory status. At the conclusion of Phase 1, patients treated with placebo were re-randomized to 1 of the 3 active treatment groups for the remaining duration of the 52-week study (ie, Phase 2). Since

the PC phase was limited to 12 weeks, interpretation of the results reported overall from BL to Week 52 and from Weeks 12 to 52 were limited.

Muscle strength scores (intention-to-treat [ITT] population)

- For the primary efficacy endpoint, all treatment groups demonstrated statistically significant improvements in muscle strength scores vs. placebo from baseline (BL) to Week 12. The least squares (LS) mean change from BL (95% confidence interval [CI]) for each treatment group and the p-values for the between-treatment difference in change from BL were as follows:
  - Deflazacort 0.9 mg/kg/day (n = 48): 0.15 (0.01, 0.28); p = 0.0173
  - Deflazacort 1.2 mg/kg/day (n = 46): 0.26 (0.12, 0.40); p = 0.0003
  - Prednisone 0.75 mg/kg/day (n = 45): 0.27 (0.13, 0.41); p = 0.0002
  - Placebo (n = 50): -0.10 (-0.23, 0.03)
- During Phase 2, only the deflazacort 0.9 mg/kg/day group maintained a statistically significant improvement in muscle strength, while the prednisone group trended in the opposite direction.
  - Deflazacort 0.9 mg/kg/day (n = 41): 0.17 (0.03, 0.31); p = 0.0044
  - Deflazacort 1.2 mg/kg/day (n = 34): 0.04 (-0.11, 0.19); p = 0.1788
  - Prednisone 0.75 mg/kg/day (n = 37): -0.12 (-0.26, 0.03)
- Overall, both deflazacort groups demonstrated greater improvements from BL to Week 52 in muscle strength scores vs. the prednisone group.
  - Deflazacort 0.9 mg/kg/day (n = 41): 0.39 (0.25, 0.54)
  - Deflazacort 1.2 mg/kg/day (n = 34): 0.38 (0.23, 0.54)
  - Prednisone 0.75 mg/kg/day (n = 37): 0.23 (0.07, 0.38)

Weight gain comparisons (ITT population)

- During the first 12 weeks of treatment, a statistically significant weight gain was demonstrated only in the prednisone group vs. placebo. The LS mean change from BL (95% CI) for each treatment group (kg) and the p-values for the between-treatment difference in change from BL to Week 12 were as follows:
  - Deflazacort 0.9 mg/kg/day (n = 48): 1.72 (0.51, 2.93); p = 0.8848
  - Deflazacort 1.2 mg/kg/day (n = 47): 1.71 (0.47, 2.94); p = 0.8921
  - Prednisone 0.75 mg/kg/day (n = 45): 3.23 (1.94, 4.52); p = 0.0459
  - Placebo (n = 50): 1.23 (0.00, 2.46)
- From Weeks 12 to 52, the deflazacort groups showed significantly smaller increases in weight vs. prednisone.
  - Deflazacort 0.9 mg/kg/day (n = 40): 3.64 (2.90, 4.38); p = 0.0003
  - Deflazacort 1.2 mg/kg/day (n = 35): 4.16 (3.37, 4.94); p = 0.0130
  - Prednisone 0.75 mg/kg/day (n = 37): 5.57 (4.76, 6.37)

- In Study 2 (MP-104-NM-002), 29 ambulatory males diagnosed with DMD and between the ages of 5 and 11 years were randomized 2:1 to receive treatment with deflazacort 2 mg/kg every 2 days (n = 18) or placebo (n = 11) for 2 years *(Angelini et al 1994)*. The primary endpoint was the change in muscle strength score from BL to Year 2 or the LoA, whichever occurred first.
  - The study failed to yield statistically significant results for the primary endpoint at the pre-determined 2-year assessment time, with a between-treatment difference in change from BL between the placebo and deflazacort groups of 5.2 (95% CI: -3.16 to 13.56; p = 0.2107).
- A 2016 Cochrane review of corticosteroids for the treatment of DMD concluded the following: *(Matthews et al 2016)*
  - RCTs provide moderate quality evidence that treatment with corticosteroids in patients with DMD vs. placebo improved muscle strength and function, including respiratory muscle strength and function, for 6 months. There was evidence of a continuing benefit on muscle strength and function at 1 year, but little RCT evidence concerning the longer-term effects of corticosteroids vs. placebo.
  - Not enough data were available to adequately compare the efficacy of prednisone and deflazacort, although there is very low quality data favoring deflazacort for less weight gain.

CLINICAL GUIDELINES

- DMD Care Considerations Working Group: Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management *(Bushby et al 2010)*
  - Glucocorticoids are the only medications currently available that slow 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.
  - 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. Particular care needs to be taken with such patients in deciding which glucocorticoid to choose, when to initiate treatment, and how best to monitor the child for any problems.
  - No generally accepted guidelines exist in the literature about the best time to initiate glucocorticoid therapy in an ambulatory boy with DMD. The panel's opinion is that the timing of initiation of glucocorticoid therapy must be an individual decision, based on functional state and also considering age and pre-existing risk factors for adverse effects (AEs). Initiation of glucocorticoid treatment is not recommended for a child who is still gaining motor skills, especially when he is under 2 years of age.
  - The typical boy with DMD continues to make progress in motor skills until approximately age 4 to 6 years, albeit at a slower rate than his peers. The eventual use of glucocorticoids should be discussed with caregivers at this stage, in anticipation of the plateau in motor skills and subsequent decline. Once the plateau phase has been clearly identified, usually at age 4 to 8 years, the clinician should propose initiation of glucocorticoids unless there are substantial reasons (such as major pre-existing risk factors for AEs) to wait until the decline phase. Starting steroids when in the full decline phase or when ambulation is more marginal is still recommended, but might be of more limited benefit.
  - 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 legal availability, cost, formulation, and perceived AE profiles. Prednisone is inexpensive and available in tablet and liquid formulations. Where available, deflazacort is more expensive and comes in fewer tablet sizes. Deflazacort might be preferred to prednisone for some patients because of the likely lower risk of weight gain.

- American Academy of Neurology (AAN) Practice guideline update summary: Corticosteroid treatment of Duchenne muscular dystrophy *(Gloss et al 2016)*
  - In children with DMD, prednisone should be offered for improving strength and pulmonary function.
  - Prednisone may be offered for improving timed motor function, reducing the need for scoliosis surgery, and delaying cardiomyopathy onset by 18 years of age.
  - Deflazacort may be offered for improving strength and timed motor function and delaying age at LoA by 1.4 to 2.5 years.
  - Deflazacort may be offered for improving pulmonary function, reducing the need for scoliosis surgery, delaying cardiomyopathy onset, and increasing survival at 5 to 15 years of follow-up.
  - Deflazacort and prednisone may be equivalent in improving motor function.
  - Prednisone may be associated with greater weight gain in the first years of treatment than deflazacort.
  - Deflazacort may be associated with a greater risk of cataracts than prednisone.
  - The preferred dosing regimen of prednisone is 0.75 mg/kg/day. Over 12 months, prednisone 10 mg/kg/weekend is equally effective, with no long-term data available. Prednisone 0.75 mg/kg/day is associated with significant risk of weight gain, hirsutism, and Cushingoid appearance.

SAFETY SUMMARY

- Contraindications
  - Hypersensitivity to deflazacort or to any components of the formulation.
    - Instances of hypersensitivity, including anaphylaxis, have occurred in patients receiving corticosteroid therapy.
- Warnings and precautions of deflazacort are similar to those of other corticosteroids (eg, prednisone) and include alterations in endocrine function, immunosuppression and increased risk of infection, alterations in cardiovascular/renal function, gastrointestinal perforation, behavioral and mood disturbances, effects on bones, ophthalmic effects, avoiding certain vaccinations, serious skin rashes, effects on growth and development, myopathy, Kaposi's sarcoma, risk of serious adverse events (SAEs) in infants because of benzyl alcohol preservative, thromboembolic events, and anaphylaxis.
- The most common AEs (≥ 10% and greater than placebo) with deflazacort use were Cushingoid appearance (33% with deflazacort vs. 12% with placebo), increased weight (20% vs. 6%), increased appetite (14% vs. 2%), upper respiratory

tract infection (12% vs. 10%), cough (12% vs. 6%), pollakiuria (12% vs. 2%), hirsutism (10% vs. 2%), central obesity (10% vs. 4%), and nasopharyngitis (10% vs. 6%).
  - In Study 1, at the Week 52 final assessment, the LS mean (95% CI) differences from BL in weight were 5.05 (4.08, 6.01; p < 0.0001 vs. prednisone), 5.60 (4.59, 6.61; p < 0.0001 vs. prednisone), and 8.45 (7.41, 9.49) for deflazacort 0.9 mg, deflazacort 1.2 mg, and prednisone, respectively.

DOSING AND ADMINISTRATION

Table 1. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Emflaza (deflazacort)	Tablets, suspension	Oral	Daily	May be taken with or without food. No dosage adjustment in renal impairment. No dosage adjustment in mild and moderate hepatic impairment; not studied in severe hepatic impairment.

See the current prescribing information for full details

CONCLUSION

- Emflaza (deflazacort) tablets and oral suspension are indicated for the treatment of DMD in patients ≥ 5 years of age. Deflazacort is a corticosteroid prodrug whose active metabolite binds glucocorticoid receptors to exert immunosuppressive and anti-inflammatory effects.
- The efficacy and safety of deflazacort were demonstrated in 2 DB, PC, MC, RCTs conducted in the 1980s-90s.
  - In Study 1 (N = 196), all of the treatment groups (deflazacort 0.9 mg/kg/day or 1.2 mg/kg/day, prednisone 0.75 mg/kg/day) demonstrated statistically significant improvements in muscle strength vs. placebo from BL to Week 12. There were significant increases in weight with prednisone vs. placebo, but no significant differences between the deflazacort groups vs. placebo at Week 12 *(Griggs et al 2016)*.
  - Study 2 (N = 29) failed to yield statistically significant results for the change in muscle strength from BL to Year 2 in patients treated with an alternate regimen of deflazacort (2 mg/kg every other day) or placebo *(Angelini et al 1994)*.
- Available DMD treatment guidelines recommend the use of glucocorticoids, which are the only medications currently available that slow the decline in muscle strength and function in DMD, which in turn reduces the risk of scoliosis and stabilizes pulmonary function *(Bushby et al 2010, Gloss et al 2016, UpToDate 2017)*.
  - 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 AE profiles. Prednisone is inexpensive and available in tablet and liquid formulations. Deflazacort is more expensive and comes in fewer tablet sizes.
  - Deflazacort might be preferred to prednisone for some patients because of the likely lower risk of weight gain.
- On the basis of extensive clinical experience, head-to-head comparisons, and available guidelines for the treatment of patients with DMD, deflazacort and prednisone appear to have similar efficacy. The selection of one agent over the other appears to rest primarily on the differences in their respective AE profiles and namely, on the limited evidence suggesting that deflazacort may be associated with a lesser increase in body weight vs. prednisone; however, this effect on weight gain may not always be undesirable among more fragile, undernourished patients with DMD.

REFERENCES

- Angelini C, Pegoraro E, Turella E, Intino MT, Pini A, Costa C. Deflazacort in Duchenne dystrophy: study of long-term effect. *Muscle Nerve*. 1994;17(4):386-91.
- Bushby K, Finkel R, Birnkrant DJ, et al; DMD Care Considerations Working Group. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. *Lancet Neurol*. 2010;9(1):77-93.
- Darras BT. Treatment of Duchenne and Becker muscular dystrophy. UpToDate Web site. 2017. www.uptodate.com. Updated July 18, 2017. Accessed August 31, 2017.
- FDA/CDER resources page. Food and Drug Administration Web site. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed September 5, 2017.
- Duchenne Muscular Dystrophy (DMD). Muscular Dystrophy Association (MDA) Web site. https://www.mda.org/disease/duchenne-muscular-dystrophy. Accessed August 31, 2017.
- Emflaza [formulary submission dossier], Northbrook, IL: Marathon Pharmaceuticals, LLC; February 2017.
- Emflaza [package insert], Northbrook, IL: Marathon Pharmaceuticals, LLC; February 2017.
- FDA Center for Drug Evaluation and Research. Emflaza Medical Review [Application Numbers 208684Orig1s000 and 208685Orig1s000]. FDA Web site. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208684,208685Orig1s000MedR.pdf. Accessed August 31, 2017.
- FDA Center for Drug Evaluation and Research. Emflaza Summary Review [Application Numbers 208684Orig1s000 and 208685Orig1s000]. FDA Web site. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208684,208685Orig1s000SumR.pdf. Accessed August 31, 2017.
- Gloss D, Moxley RT 3rd, 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):465-72.
- 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.
- Matthews E, Brassington R, Kuntzer T, Jichi F, Manzur AY. Corticosteroids for the treatment of Duchenne muscular dystrophy. *Cochrane Database Syst Rev*. 2016;(5):CD003725.

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