Therapeutic Class Overview
Duchenne muscular dystrophy (DMD) Agents

INTRODUCTION

- Duchenne muscular dystrophy (DMD) is 1 of 4 conditions known as dystrophinopathies, which are inherited, X-linked myopathic disorders due to a defect in the dystrophin gene that results in the primary pathologic process of muscle fiber degradation. The hallmark symptom is progressive weakness (*Darras 2018[a], Darras 2018[b], Muscular Dystrophy Association [MDA] 2019)*.
  - The other 3 conditions include: Becker muscular dystrophy (BMD), which is a mild form of DMD; an intermediate presentation between BMD and DMD; and DMD-associated dilated cardiomyopathy, which has little or no clinical skeletal or muscle disease (*MDA 2019*).
- DMD symptom onset is in early childhood, usually between the ages of 2 and 3 years old. The proximal muscles are affected first, followed by the distal limb muscles. Generally, the lower external muscles will be affected before the upper. The affected child may have difficulties jumping, walking, and running (*MDA 2019*).
- The prevalence of DMD ranges from 1 to 2 per 10,000 live male births; female-manifesting carriers are rarer, but can present with a range of symptoms that vary in their severities (*Birnkrant et al 2018, Darras 2018[a], Emflaza Food and Drug Administration [FDA] Medical Review 2017*).
- The clinical course and lifespan of patients with DMD is relatively short. Individuals are usually confined to a wheelchair by age 13, and many die in their late teens or twenties from respiratory insufficiency or cardiomyopathy. Although survival until adulthood is more common now, very few patients survive past the 3rd decade (*Darras 2018[a]*).
- Glucocorticoids (GCs) are the mainstay of therapy for DMD, including prednisone and deflazacort. Their beneficial effects include improving motor and pulmonary function, reducing the risk of scoliosis, delaying loss of ambulation (LoA), possible delay of cardiomyopathy progression, and improving overall survival (*Shieh et al 2018*).
  - Though not FDA-approved for DMD, prednisone is used off-label and considered a main drug of treatment.
- There are 3 FDA-approved agents for DMD which will be the focus of this overview: Emflaza (deflazacort), Exondys 51 (eteplirsen), and Vyondys 53 (golodirsen).
  - About 13% of patients with DMD carry the mutation for which eteplirsen is a potential therapy (*Birnkrant et al 2018).*
  - About 8% of patients with DMD carry the mutation for which golodirsen is a potential therapy (*Sarepta news release 2019[b]*).
- Three potential new therapies for DMD are in the emerging pipeline with ongoing Phase 3 trials.
  - Translarna (ataluren), an investigational new drug developed for DMD caused by nonsense mutations, was not approved by the FDA in October 2017. In a complete response letter (CLR) for the new drug application (NDA), the FDA requested additional evidence of effectiveness from well-controlled clinical trials. In February 2018, the FDA denied an appeal from the manufacturer and suggested that the currently enrolling Study-041 could serve as a confirmatory post-approval trial required in connection with the accelerated approval framework (*PTC Therapeutics news release 2017, PTC Therapeutics news release 2018).*
  - Golodirsen, developed for the treatment of DMD in patients with mutations amenable to exon 53 skipping, was also rejected by the FDA in August 2019. A CLR raised concerns over the risk of infections upon injection of the therapy and the possibility of toxicity to the kidneys. However, on December 12, 2019 the drug was granted accelerated approval in patients with confirmed mutation amenable to exon 53 skipping (*Sarepta news release 2019[a], Sarepta news release 2019[b]*).
  - Casimersen, developed to treat DMD in patients with mutations amenable to exon 45 skipping, is awaiting FDA review.
- Medispan Classes:
  - Endocrine and metabolic agents; corticosteroids; glucocorticosteroids
  - Neuromuscular agents; muscular dystrophy agents

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Emflaza (deflazacort)	-
Exondys 51 (eteplirsen)	-
Vyondys 53 (golodirsen)	-

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Emflaza (deflazacort)	Exondys 51 (eteplirsen)*	Vyondys 53 (golodirsen)*
Treatment of DMD in patients 2 years of age and older	✔		
Treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping		✔	
Treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping			✔

*Accelerated approval was based on an increase in dystrophin in skeletal muscle observed in some patients treated with eteplirsen and golodirsen. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

(*Prescribing information: Emflaza 2017, Exondys 51 2018, Vyondys 53 2019)*

- 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

- There has been considerable experience using Emflaza (deflazacort) and other corticosteroids for the management of patients with DMD. A number of observational studies have been conducted to assess the long-term effects of corticosteroid use on muscle strength, the ability to walk, and on weight gain, among other outcomes. Overall, these studies concluded that patients taking steroids were significantly more functional and performed better on testing vs untreated patients and confirmed the prolongation of ambulation from a mean of 10.0 years in individuals treated with less than 1 year of corticosteroids to a mean of 11.2 years in individuals treated with daily prednisone and 13.9 years in individuals taking daily deflazacort (*Balaban et al 2005, Bello et al 2015, Kim et al 2015*).
- A Cochrane systematic review of 12 randomized controlled trials (RCTs) (N = 667) found that they provided moderate quality evidence for treatment with corticosteroids in patients with DMD. Compared to placebo, corticosteroids improved muscle strength and function (including respiratory muscle strength and function) for 6 months, with continued evidence of benefit at 1 year. There is no evidence other than from non-randomized trials to establish the effect of corticosteroids on prolongation of walking (*Matthews et al 2016*).
- The safety and efficacy of deflazacort for the treatment of DMD were demonstrated in 2 pivotal trials conducted in the 1980s and 1990s (*Angelini et al 1994, Emflaza Formulary Submission Dossier 2017, Griggs et al 2016)*.
  - A 52-week, Phase 3, double-blind (DB), placebo-controlled (PC), multi-center (MC), RCT (N = 196) was conducted to assess the safety and efficacy of deflazacort and prednisone vs placebo in boys aged 5 to 15 years old with DMD. For the first 12 weeks of the study (ie, Phase 1), patients were randomized to 1 of 4 groups (deflazacort 0.9 mg/kg/day, deflazacort 1.2 kg/mg/day, prednisone 0.75 mg/kg/day, or placebo). For the remainder of the study through week 52 (ie, Phase 2), patients initially randomized to placebo were re-randomized to 1 of the 3 active treatments (deflazacort 0.9 mg/kg/day, deflazacort 1.2 kg/mg/day, or prednisone 0.75 mg/kg/day). For the primary efficacy endpoint, all treatment groups demonstrated statistically significant improvements in muscle strength vs placebo from baseline to week 12. During Phase 2, only the deflazacort 0.9 mg/kg/day group maintained a statistically significant improvement in muscle strength vs prednisone-treated patients; however, both deflazacort groups outperformed the prednisone group by week 52 (secondary efficacy endpoint) (*Griggs et al 2016*).
    - In the opinion of the FDA, the results for the change from week 12 to week 52 were not interpretable. The larger increase in muscle strength score from week 12 to week 52 in the deflazacort 0.9 mg/kg/day group was mostly due to a lower score at week 12 in this group. Because the groups were not comparable at week 12, the comparisons of the treatment effect from weeks 12 to 52 were not considered meaningful (*Emflaza FDA Summary Review 2016).*

        - At week 52, patients taking prednisone had significantly more weight gain than both deflazacort groups. The most frequent adverse effects (AEs) reported were: Cushingoid appearance, erythema, hirsutism, increased weight, headache, and nasopharyngitis.
    - A 2-year, Phase 3, DB, PC, MC, RCT (N = 29) was conducted to evaluate the change in muscle strength from baseline to 2 years or LoA, whichever occurred first, in boys aged 5 to 11 years old with DMD and symptom onset before age 5. By year 2, the study failed to show a statistically significant result for change in muscle strength, possibly because of a limited number of patients remaining in the placebo arm (12 patients vs 3 patients). The median time to LoA was statistically significant for deflazacort vs placebo (63.0 months [95% CI: 35.1 to not estimable] vs 31.9 months [95% CI: 13.6 to 54.6], p = 0.0052) (*Angelini et al 1994*).
- Exondys 51 (eteplirsen) was evaluated in 3 clinical studies in patients with a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.
    - Study 201 was a 24-week, Phase 2b, DB, PC, RCT (N = 12) that evaluated eteplirsen's ability to induce dystrophin production (surrogate endpoint) and improve distance walked on the 6-minute walk test (6MWT, clinical outcome) in boys aged 7 to 13 years old that were stable on corticosteroid treatment for at least 6 months. Patients were randomized to weekly intravenous (IV) infusions of 30 or 50 mg/kg/wk eteplirsen or placebo for 24 weeks (n = 4/group). Placebo patients switched to 30 or 50 mg/kg eteplirsen (n = 2/group) at week 25. Study 202 was a 212-week, ongoing Phase 2, open-label (OL), MC extension study; all 12 patients who participated in Study 201 continued treatment in Study 202 (*Mendell et al 2013*).
        - The Study 201 authors concluded that at week 24, dystrophin-positive fibers increased by 23% from baseline in patients treated with 30 mg/kg eteplirsen, with no significant increases in the placebo group (p ≤ 0.002). Greater increases continued to occur by week 48 (52% and 43% in the 30 and 50 mg/kg groups, respectively). The authors also concluded that 6 ambulation-evaluable patients taking eteplirsen demonstrated an increase in the 6MWT (67.3 m, p ≤ 0.001) vs placebo.
        - The average dystrophin protein level after 180 weeks of treatment with eteplirsen was 0.93% of the normal dystrophin level in healthy subjects (*Exondys 51 prescribing information 2018*).
            - The FDA noted that for the week 180 analysis, archived pre-treatment muscle biopsy samples were available for re-analysis from only 3 patients in Studies 201/202, and samples from controls were also obtained from different muscle groups than the eteplirsen-treated patients; therefore, the true change in dystrophin was difficult to estimate (*Exondys 51 FDA Summary Review 2016).*
            - In contrast to the conclusions of Mendell et al, the FDA found no significant difference in the change in 6MWT distance between patients treated with eteplirsen and those treated with placebo in Study 201. Additionally, Study 202 failed to provide evidence of a clinical benefit when compared to the external control group (primary endpoint, week 48) (*Exondys 51 FDA Summary Review 2016).*
    - A confirmatory Phase 3, 144-week, OL, MC study (PROMOVI) was conducted in 109 ambulatory males between ages 7 to 16 years old on a stable dose of corticosteroids for at least 24 weeks. Patients in the treated group (DMD amenable to exon 51 skipping) received once weekly IV infusions of 30 mg/kg eteplirsen for 96 weeks, followed by a safety extension (not to exceed 48 weeks). Patients in the untreated group did not receive treatment. The primary outcome was change in 6MWT distance from baseline to 96 weeks (*Alfano et al 2019*).
        - Results at 48 weeks (N = 13) showed a median increase in dystrophin levels from 0.16% at baseline to 0.44% (p < 0.05). The median increase after 48 weeks was 0.1%. The study completed in 2019, and full results are pending.
    - Vyondys 53 (golodirsen) was granted accelerated approval based on a 2-part clinical study (*FDA news release 2019, Sarepta news release 2019[b], Vyondys 53 prescribing information 2019*).
        - Part 1 was a DB, PC, dose-titration study (N = 12). Patients were randomized 2:1; 8 patients received 4 escalating dose levels of golodirsen IV (ranging from 4 mg/kg/week to 30 mg/kg/week) for 2 weeks at each level, while 4 patients received placebo.
        - Part 2 was an OL study that included the 12 patients from Part 1, plus 13 additional treatment-naïve patients with DMD amenable to exon 53 skipping. Patients were given golodirsen at a dose of 30 mg/kg/week. Results showed that dystrophin levels increased (on average) from 0.10% of normal at baseline to 1.02% of normal after 48 weeks of treatment (mean change in dystrophin of 0.92% of normal levels, p < 0.001).
        - This study only evaluated a surrogate endpoint; a clinical benefit of golodirsen was not established. An ongoing, confirmatory Phase 3 trial (ESSENCE) is currently being conducted to assess whether golodirsen improves motor function in patients with DMD amenable to exon 53 skipping.

CLINICAL GUIDELINES

- DMD Care Considerations Working Group: Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management *(Birnkrant et al 2018).*
  - Physiotherapy and treatment with GCs is the mainstay of DMD treatment and should continue after LoA. The benefits of long-term GC therapy have been shown to include LoA at a later age, preserved upper limb and respiratory function, and avoidance of scoliosis surgery.
  - Recent studies confirm the benefits of starting GCs in younger children, and the consensus is to begin steroid regimens before significant physical decline. Recommended starting doses include prednisone or prednisolone 0.75 mg/kg/day, or deflazacort 0.9 mg/kg/day. Patients should be reassessed at regular intervals to monitor functional decline and consider therapy updates.
- American Academy of Neurology (AAN) Practice guideline update summary: Corticosteroid treatment of DMD (*Gloss et al 2016*).
  - The ideal time to start and stop therapy is not currently known.
  - 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.
  - Calcium and vitamin D intake are optimized and encouraged in clinical practice, as these children have several risk factors for low bone density and fractures, such as chronic corticosteroid use and decreased weight-bearing activities.
    - The American College of Rheumatology Task Force osteoporosis guideline recommends calcium and vitamin D supplementation for patients taking corticosteroids (any dose with an anticipated duration of ≥ 3 months) in order to maintain a total calcium intake of 1200 mg/day and vitamin D intake of 800 IU/day through dietary sources, supplementation, or both.

SAFETY SUMMARY

Emflaza (deflazacort)

- 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 AEs in infants because of the 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%).

Exondys 51 (eteplirsen)

- No contraindications known at this time.
- Warnings/precautions:

- Hypersensitivity reactions: Reactions including pyrexia, flushing, cough, dyspnea, bronchospasm, rash, urticaria, and hypotension have occurred in patients. If hypersensitivity reactions occur, appropriate medical treatment should be instituted, and slowing of the infusion or interruption of eteplirsen therapy should be considered.

- The most common AEs (incidence ≥ 35% and higher than placebo) were balance disorder and vomiting.

Vyondys 53 (golodirsen)

- No contraindications known at this time.
- Warnings/precautions:
  - Hypersensitivity reactions: Hypersensitivity reactions, including rash, pyrexia, pruritus, urticaria, dermatitis, and skin exfoliation, have occurred in patients receiving golodirsen. If a hypersensitivity reaction occurs, appropriate medical treatment should be instituted and slowing of the infusion or interruption of golodirsen therapy should be considered.
  - Renal toxicity: Based on animal data, golodirsen may cause renal toxicity. Renal function should be monitored; creatinine may not be a reliable measure of renal function in DMD patients.
- The most common AEs (incidence ≥ 20% and higher than placebo) were headache, pyrexia, fall, abdominal pain, nasopharyngitis, cough, vomiting, and nausea.

DOSING AND ADMINISTRATION

Table 3. 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; has not been studied in severe hepatic impairment
Exondys 51 (eteplirsen)	Injection	IV	Once weekly	Administer IV infusion over 35 to 60 minutes If a hypersensitivity reaction occurs, consider slowing the infusion or interrupting therapy.
Vyondys 53 (golodirsen)	Injection	IV	Once weekly	Administer IV infusion over 35 to 60 minutes If a hypersensitivity reaction occurs, consider slowing the infusion or interrupting therapy.

See the current prescribing information for full detail

CONCLUSION

- GCs remain the mainstay of therapy for DMD, and are currently recommended for all patients. The benefits of long-term GC therapy have been shown to include LoA at a later age, preserved upper limb and respiratory function, and avoidance of scoliosis surgery *(Birnkrant et al 2018*).
- Emflaza (deflazacort) tablets and oral suspension are indicated for the treatment of DMD in patient's ≥ 5 years of age.
- The efficacy and safety of deflazacort were demonstrated in 2 pivotal DB, PC, MC, RCTs conducted in the 1980s and 1990s. Results showed that daily use of either deflazacort or prednisone was effective in preserving muscle strength over a 12-week period (*Griggs et al 2016).*

- Exondys 51 (eteplirsen) is indicated for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping; this includes only about 13% of the overall patient population. Similarly, Vyondys 53 (golodirsen) is indicated for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping; this includes only about 8% of the overall patient population.
  - These indications were approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with eteplirsen or golodirsen.
  - Continued approval for these indications may be contingent upon verification of a clinical benefit in confirmatory trials (ie, PROMOVI, ESSENCE). Methodological flaws in the study designs etepliren were brought to light during the FDA review process and have called into question whether the production of dystrophin is high enough to provide a true clinical benefit for patients with DMD.

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