OPTUMRx

Therapeutic Class Overview
Duchenne muscular dystrophy (DMD) Agents

INTRODUCTION

- Duchenne muscular dystrophy (DMD) is a fatal, X-linked neuromuscular disorder caused by *DMD* gene mutations that result in the absence or near-absence of functional dystrophin protein in muscle cells and progressive loss of skeletal and cardiac function (*Institute for Clinical and Economic Review [ICER] 2019*).
  - DMD is the most common pediatric muscular dystrophy, with an incidence of about 400 to 600 cases per year and a prevalence of approximately 6000 males in the US (*ICER 2019*).
- Diagnosis of DMD typically occurs in early childhood, with symptoms beginning around 3 to 5 years of age. Early symptoms include muscle weakness, clumsiness, difficulty with rising from a squatted position (Gower's sign), and difficulty going up and down stairs (*ICER 2019*).
  - DMD patients may also have developmental delay, behavioral issues, impaired growth, delayed puberty, adrenal insufficiency, and gastrointestinal complications (eg, dysphagia and gastroparesis) (*ICER 2019*).
  - Osteoporosis with resultant fractures may occur from the disease itself and as an AE of glucocorticoid therapy (*ICER 2019*).
  - Loss of ambulation typically occurs by 12 years of age. Fatal respiratory or cardiac complications frequently develop in the second or third decade of life, and many deaths occur in the setting of an acute infection (*Food and Drug Administration [FDA] Vyondys 53 summary review 2020, ICER 2019*).
- Dystrophin forms an important part of the glycoprotein complex, strengthening and connecting muscle fibers in skeletal and cardiac muscle. Lack of dystrophin results in degeneration of muscle fibers, inflammation, and ultimately replacement of muscle by fibrotic and adipose tissue (*ICER 2019*).
- DMD may be caused by more than 2000 mutations in the *DMD* gene that result in loss of expression or expression of nonfunctional dystrophin protein. An estimated 70% of DMD patients have single- or multi-exon deletions or duplications that are amenable to detection via genetic testing. Disease severity appears to vary by mutation, resulting in a heterogeneous population with differing rates of progression (*ICER 2019*).
- Becker muscular dystrophy (BMD) has a similar presentation to DMD, but typically has a later onset (5 to 60 years of age) and a milder clinical course. BMD patients typically remain ambulatory into adult life and survive beyond the age of 30 years (*Darras 2020*).

Table 1. Clinical features of DMD vs BMD (*Darras 2020*)

	Duchenne muscular dystrophy	Becker muscular dystrophy
Clinical course	Severe	Mild
Age of onset	3 to 5 years	5 to 60 years
Loss of ambulation	Early teens	Adulthood
Common *DMD* gene mutations	Out-of-frame exon deletion/ duplication, nonsense mutation	In-frame exon deletion/ duplication, missense mutation
Dystrophin expression by immunohistochemistry	Absent	Reduced
Dystrophin expression by western blot	< 5% of normal	> 20% of normal

- There are currently no therapies available to cure DMD or halt disease progression (*Messina and Vita 2018*).
- Corticosteroids are the mainstay of pharmacologic therapy for DMD. Early initiation of corticosteroids has been associated with prolonged ambulation, decreased contractures and deformities, and prolonged function and participation in activities of daily living. Steroids are usually begun early in the disease course, prior to substantial physical decline. AEs of corticosteroids include weight gain, hirsutism, decreased bone density with increased risk of fracture, and cataracts (*ICER 2019, Messina and Vita 2018*).
  - In 2017, Emflaza (deflazacort) was the first corticosteroid FDA approved specifically for DMD. In clinical trials of DMD patients, treatment with deflazacort offered similar benefits to prednisone and was associated with less weight gain; however, deflazacort may be associated with an increased risk of cataracts compared with prednisone (*ICER 2019*).

- Many patients with DMD carry mutations in the *DMD* gene that cause misalignments in the transcription reading frame, leading to nonfunctional or absent dystrophin. As part of RNA synthesis, exons are connected to generate mRNA that encodes dystrophin, and mutations in a single exon can disrupt all downstream synthesis of protein if the reading frame is disrupted (*ICER 2019*).
  - Exon-skipping therapies are antisense oligonucleotides that prevent mutated exons from being transcribed, allowing for downstream exons to be transcribed in the correct reading frame. The remaining exons form a shortened mRNA that encodes a truncated, partially functional dystrophin protein. Animal models and anecdotal data suggest that restoration of small amounts of dystrophin (between 2 to 4% of normal) may be beneficial in slowing DMD progression; however, clinical correlation has yet to be established (*ICER 2019*).
- There are 4 exon-skipping therapies with FDA approval for DMD. Each therapy received biomarker-based accelerated approval based on increases in dystrophin protein expression in muscle biopsy tissue. There is no consensus on the threshold of dystrophin expression in skeletal muscle fibers required to increase or to normalize muscle function in patients with DMD. The clinical benefit of exon-skipping therapies has not been established and will be evaluated in ongoing confirmatory studies (*FDA Amondys 45 summary review 2021*).
  - Exondys 51 (eteplirsen) was the first exon-skipping therapy to receive FDA approval for DMD in 2016. It remains the only therapy indicated for DMD patients with mutations amenable to exon 51 skipping (approximately 13% of the DMD population) (*FDA Exondys 51 summary review 2016*).
    - Prior to approval, the FDA's Peripheral and Central Nervous System Drugs Advisory Committee voted against the efficacy of eteplirsen for DMD based on a single historically-controlled study and against the availability of substantial evidence from adequate and well controlled studies that eteplirsen induced dystrophin production to a level that was reasonably likely to predict clinical benefit (*FDA Exondys 51 summary review 2016*).
    - An appeal of the decision to approve eteplirsen convened the Agency Scientific Dispute Process Review Board, whose Chair ultimately agreed with the conclusions of the Director of the Office of Drug Evaluation I (ODE-1) that the overall evidence derived from the limited clinical development program did not support that the levels of dystrophin produced by eteplirsen were reasonably likely to provide clinical benefit (*FDA Vyondys 53 clinical review 2020*).
  - Vyondys 53 (golodirsen) and Viltepso (viltolarsen) were approved in 2019 and 2020, respectively, for DMD patients with mutations amenable to exon 53 skipping (approximately 9% of the DMD population) (*FDA Viltepso clinical review 2020, FDA Vyondys 53 summary review 2020*).
    - Golodirsen was initially issued a complete response letter issued based on the determination that the small, unverified benefit with golodirsen did not outweigh the risks for renal toxicity and serious infections related to drug delivery. FDA approval of golodirsen was granted upon appeal (*FDA Vyondys 53 clinical review 2020*).
  - Amondys 45 (casimersen) was approved in 2021 as the only therapy for DMD patients with mutations amenable to exon 45 skipping (approximately 8% of the DMD population) (*FDA Amondys 45 summary review 2021*).
- Ataluren is an oral therapy that promotes ribosomal read-through of nonsense (stop) mutations, which are present in 10 to 15% of patients with DMD. Although not approved by the FDA, ataluren is available to patients in 23 countries through either expanded access programs or commercial sales (*Darras 2021*).
- Clinical trials for investigational DMD therapies are ongoing, including gene transfer by intravascular administration of recombinant adeno-associated viral vectors that carry microdystrophin or minidystrophin genes (*Darras 2021*).
- Medispan classes: Neuromuscular agents, muscular dystrophy agents; Corticosteroids, glucocorticosteroids

Table 2. Medications Included Within Class Review

Drug	Generic Availability
Amondys 45 (casimersen)	-
Emflaza (deflazacort)	-
Exondys 51 (eteplirsen)	-
Vyondys 53 (golodirsen)	-
Viltepso (viltolarsen)	-

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

Table 3. FDA-Approved Indications

Indication	Amondys 45 (casimersen)	Emflaza (deflazacort)	Exondys 51 (eteplirsen)	Vyondys 53 (golodirsen)	Viltepso (viltolarsen)
Treatment of DMD in patients ≥ 2 years of age		✔			
Treatment of DMD in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 45 skipping	✔				
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				✔	✔

(*Prescribing information: Amondys 45 2021, Emflaza 2021, Exondys 51 2020, Viltepso 2021, Vyondys 53 2021*)

- 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

Corticosteroids (deflazacort)

- There is considerable experience with the use of Emflaza (deflazacort) and other corticosteroids for the management of patients with DMD. Several observational studies have assessed the long-term effects of corticosteroid use on muscle strength, ambulation, weight gain, and other outcomes. Overall, these studies concluded that patients taking steroids performed better on functional outcome testing and experienced prolonged ambulation vs untreated patients (*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 moderate quality evidence supporting 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 was no evidence other than from non-randomized trials to establish the effect of corticosteroids on prolongation of ambulation (*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, 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 (*FDA Emflaza summary review 2017).*

- 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 loss of ambulation, 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 loss of ambulation was significantly longer in patients treated with 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*).

Exon-skipping therapies (casimersen, eteplirsen, golodirsen, viltolarsen)

- 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 (*Exondys 51 prescribing information 2020*).
  - Study 201 was a 24-week, Phase 2b, DB, PC, RCT (N = 12) that evaluated the surrogate outcome of dystrophin production and the clinical efficacy outcome of 6-minute walk test (6MWT) distance in boys aged 7 to 13 years of age that were stable on corticosteroid treatment for at least 6 months. Patients were randomized to weekly intravenous (IV) infusions of eteplirsen 30 or 50 mg/kg/wk or placebo for 24 weeks (n = 4 for each group). Patients in the placebo group were switched to 30 or 50 mg/kg of eteplirsen (n = 2 for each group) at week 25. Study 202 was a 212-week, 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 meters, p ≤ 0.001) vs placebo (*Mendell et al 2013*).
    - The mean dystrophin protein expression after 180 weeks of treatment with eteplirsen was 0.93% of the normal dystrophin level in healthy subjects (*Exondys 51 prescribing information 2020*).
      - 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 (*FDA Exondys 51 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) (*FDA Exondys 51 summary review 2016*).
    - Long-term results from Study 201/202 demonstrated attenuation in pulmonary function decline (p < 0.001) and fewer patients with loss of ambulation at 4 years (17% vs 88%; p = 0.007) with eteplirsen (n = 12) compared with an untreated natural history control group (n = 20) of DMD patients amenable to exon 51 skipping from the Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study (DNHS) matched for baseline characteristics (*McDonald et al 2020*).
  - The Phase 3, OL PROMOVI trial (Study 301) was designed to evaluate the primary endpoint of 6MWT distance in 79 DMD patients treated with eteplirsen for 96 weeks compared with 30 patients in an untreated control group of DMD patients with mutations that were not amenable to exon 51 skipping (*ClinicalTrials.gov Web site*).
    - Accelerated approval of eteplirsen was based on western blot analyses of 13 patients enrolled in PROMOVI, which was ongoing at the time of FDA review. Among the 12 patients with evaluable results, mean dystrophin expression increased from 0.157% of normal at baseline to 0.440% of normal at Week 48 (mean change from baseline, 0.283%; p = 0.008). Overall, 8 (67%) patients experienced a change in dystrophin of ≤ 0.25%; only 1 patient (8%) experienced an increase > 1% of normal (*FDA Exondys 51 medical review 2016*).
    - The primary efficacy analysis was performed in all patients with a baseline 6MWT distance of 300 to 450 meters and ≥ 1 post-baseline functional assessment. The mean change from baseline to week 96 in 6MWT distance was −117.91 meters in 65 evaluable patients treated with eteplirsen and −133.56 meters in 9 evaluable patients in the untreated control group. The proportion of patients with loss of ambulation at week 96 was 17.9% in 67 evaluable

eteplirsen-treated patients, compared to 5.0% in 20 evaluable patients in the untreated control group (*ClinicalTrials.gov Web site*).
    - According to a poster presented at the World Muscle Society Virtual Congress, PROMOVI included a flawed comparison of eteplirsen-treated patients with a mismatched control arm that consisted entirely of patients with mutations not amenable to exon 51 skipping. Inadequate choice of control group became clear after study initiation, as emerging natural history data demonstrated patients with different mutations have different disease trajectories. Additionally, the control arm did not retain enough patients (15 of 30 completed the study) to allow for statistically and clinically meaningful comparisons (*McDonald et al 2020*).
  - The confirmatory study for eteplirsen (MIS51ON; NCT03992430) was initiated in 2020 with an estimated completion date in 2026. The randomized, DB phase will evaluate the safety and efficacy of a high dose of eteplirsen compared to the FDA-approved dose of 30 mg/kg IV weekly (*ClinicalTrials.gov Web site*).
- Vyondys 53 (golodirsen) was evaluated in SKIP-NMD, a 2-part, Phase 1/2 trial that enrolled ambulatory boys aged 6 to 15 years with DMD caused by out-of-frame deletions amenable to exon 53 skipping. Part 1 (n = 12) was a 12-week, Phase 1, DB, PC, dose-escalation RCT that established the safety of golodirsen. Part 2 of SKIP-NMD was a 168-week, Phase 2, OL evaluation of efficacy with golodirsen (*Frank et al 2020*).
  - Accelerated approval of golodirsen was based on the surrogate endpoint of dystrophin expression assessed by western blot. At interim analysis (n = 25), mean dystrophin expression increased from 0.095% of normal at baseline to 1.019% of normal at Week 48 (mean change from baseline, 0.924%; p < 0.001) (*Frank et al 2020*).
  - For the primary efficacy outcome of 6MWT distance, the mean change from baseline to 144 weeks was −99.0 meters in 22 evaluable patients treated with golodirsen and −160.8 meters in 6 evaluable patients who were not amenable to exon 53 skipping and did not receive treatment (*ClinicalTrials.gov Web site*).
  - The confirmatory study for golodirsen (ESSENCE; NCT02500381) is an ongoing Phase 3 trial with a 96-week, DB, PC phase followed by a 48-week OL phase with an estimated completion date in 2023. The primary endpoint will be the change in 6MWT distance from baseline to Week 96 (*ClinicalTrials.gov Web site*).
- Viltepso (viltolarsen) was evaluated in a 2-part, Phase 2, MC trial that enrolled 16 ambulatory boys aged 4 to 9 years with DMD amenable to exon 53 skipping. Two doses of viltolarsen (40 mg/kg/week [unapproved dose] and 80 mg/kg/week [approved dose]) were evaluated as add-on therapy to a stable dose of glucocorticoids. Part 1 was a 4-week, randomized, DB, PC period that established the safety of viltolarsen. Part 2 was a 20-week, OL treatment period that evaluated the efficacy and safety of low-dose and high-dose viltolarsen (*Clemens et al 2020*).
  - Accelerated approval of viltolarsen was based on an increase in dystrophin from 0.3% of normal at baseline to 5.7% of normal at week 25 with low-dose viltolarsen (mean change, 5.4%; p < 0.001), and from 0.6% of normal at baseline to 5.9% of normal at week 25 with high-dose viltolarsen (mean change, 5.3%; p = 0.01). Assessment of functional outcomes demonstrated improvement or stabilization of motor function with viltolarsen (n = 16) compared to an external natural history control group (n = 65) from the CINRG DNHS matched for age and treatment (*Clemens et al 2020*).
  - The confirmatory RACER53 trial (NCT04060199) for viltolarsen is an ongoing Phase 3, DB, PC, MC, RCT with an estimated completion date in 2024. The primary outcome will be the change from baseline to Week 48 in the time to stand test. Other functional outcomes include the time to run/walk 10 meters test, 6MWT, North Star Ambulatory Assessment (NSAA), and time to climb 4 steps test (*ClinicalTrials.gov Web site*).
- Amondys 45 (casimersen) was evaluated in the ongoing 96-week, Phase 3, randomized, DB, PC, MC ESSENCE trial that will serve as the confirmatory trial for both casimersen and golodirsen (*FDA Amondys 45 clinical review 2021*).
  - The casimersen arm of the ESSENCE study enrolled boys 7 to 13 years of age with a clinical diagnosis of DMD and a documented mutation amenable to exon 45 skipping. Key inclusion criteria included a mean 6MWT distance ≥ 300 and ≤ 450 meters, stable pulmonary and cardiac function, and stable corticosteroid therapy for ≥ 24 weeks (*FDA Amondys 45 clinical review 2021*).
  - Accelerated approval of casimersen was based on an interim analysis of the ESSENCE trial in 43 patients randomized to receive casimersen (n = 27) or placebo (n = 16) once weekly via IV infusion for 48 weeks. Mean dystrophin protein expression increased from 0.93% of normal levels at baseline to 1.74% at week 48 in the casimersen group (mean change from baseline, 0.81%; p < 0.001), as compared to 0.54% of normal at baseline to 0.76% at week 48 in the placebo group (mean change from baseline, 0.22%; p = 0.089). The between-group difference in dystrophin expression with casimersen vs placebo was 0.59% (p = 0.004) (*FDA Amondys 45 clinical review 2021*).

Table 4. FDA-approved exon-skipping therapies for DMD (*ClinicalTrials.gov Web site, Exondys 51 prescribing information 2020, FDA Amondys 45 clinical review 2021, ICER 2019, Viltepso prescribing information 2021, Vyondys 53 prescribing information 2021*)

Exon skipped	Amenable DMD Population	Drug	Manufacturer	Accelerated Approval	Dystrophin*	Confirmatory trial (Estimated completion date)
45	8%	**Amondys 45** (casimersen)	Sarepta	2021	0.81%	ESSENCE (2023)
51	13%	**Exondys 51** (eteplirsen)		2016	0.28%	MIS51ON (2026)
53	9%	**Vyondys 53** (golodirsen)		2019	0.92%	ESSENCE (2023)
		Viltepso (viltolarsen)	NS Pharma	2020	5.3%†	RACER53 (2024)

* Mean change from baseline in dystrophin measured by western blot as reported in the prescribing information
† Differences in the western blot assay methodology may prevent meaningful comparisons across studies

CLINICAL GUIDELINES

- **DMD Care Considerations Working Group: Diagnosis and management of DMD, part 1: Diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management** (*Birnkrant et al 2018*)
  - The DMD Care Considerations Working Group was supported by the CDC with involvement of the TREAT-NMD network for neuromuscular diseases, the Muscular Dystrophy Association, and Parent Project Muscular Dystrophy.
    - The guidance was not conventionally evidence based, as few large-scale RCTs have been completed for DMD, with the exception of corticosteroid studies.
    - No recommendations were provided to inform the place in therapy for eteplirsen, golodirsen, viltolarsen, or casimersen.
  - Consistent and reproducible clinical assessments of neuromuscular function performed by trained practitioners underpin the management of DMD.
    - The NSAA and timed function tests should be assessed every 6 months. They have high validity and reliability, as well as correlation between tests across time, minimum clinically important differences, and predictive capabilities regarding functional motor changes that are important in monitoring clinical progression and assessing new and emerging therapies.
    - Before 7 years of age, gains might occur in the 6MWT and timed function tests. After 7 years of age, a 6MWT distance < 325 meters and a mean linearized NSAA of 34 or less (raw score of 9) have been associated with greater functional decline in ambulation over the subsequent 12 months.
  - Physiotherapy and glucocorticoids are the mainstays of DMD treatment and should continue after loss of ambulation.
    - The benefits of long-term glucocorticoid therapy include loss of ambulation at a later age, preserved upper limb and respiratory function, and avoidance of scoliosis surgery.
    - Although the benefits of glucocorticoid therapy are well established, uncertainty remains about which glucocorticoids are best and at what doses.
  - Although the DMD Care Considerations Working Group acknowledged the FDA approval of eteplirsen, no specific recommendations were provided.

- **American Academy of Neurology (AAN) − Practice guideline update summary: Corticosteroid treatment of DMD** (*Gloss et al 2016, reaffirmed 2019*)
  - The AAN recommendations are focused on corticosteroid therapy; no recommendations are provided regarding exon-skipping therapies.
  - In children with DMD, prednisone should be offered to improve strength (Level B) and pulmonary function (Level B).
  - Prednisone may be offered to improve timed motor function (Level C), reducing the need for scoliosis surgery (Level C), and delaying cardiomyopathy onset by 18 years of age (Level C).

- Deflazacort may be offered to improve strength and timed motor function and delay age at loss of ambulation by 1.4 to 2.5 years (Level C). Deflazacort may be offered to improve pulmonary function, reduce the need for scoliosis surgery, delay cardiomyopathy onset, and increase survival at 5 to 15 years of follow-up (Level C for each).
- Deflazacort and prednisone may be equivalent in improving motor function (Level C).
- Prednisone may be associated with greater weight gain in the first years of treatment than deflazacort (Level C).
- Deflazacort may be associated with a greater risk of cataracts than prednisone (Level C).

SAFETY SUMMARY

Corticosteroids (deflazacort)

- Deflazacort is contraindicated in patients with known hypersensitivity to deflazacort or to any of the inactive ingredients.
- Warnings and precautions for 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%).

Exon-skipping therapies (casimersen, eteplirsen, golodirsen, viltolarsen)

- There are no labeled contraindications to any of the exon-skipping therapies.
- Eteplirsen and golodirsen have a labeled warning for hypersensitivity reactions.
- Casimersen, golodirsen, and viltolarsen have warnings for kidney toxicity.
  - Although kidney toxicity was not reported in clinical trials with casimersen, golodirsen, or viltolarsen, it was observed in animal studies with these agents and in human studies with other antisense oligonucleotides.
- The most common AEs with exon-skipping therapies included:
  - Casimersen (incidence ≥ 20% and ≥ 5% higher than placebo): Upper respiratory tract infection, cough, pyrexia, headache, arthralgia, and oropharyngeal pain.
  - Eteplirsen (incidence ≥ 35% and higher than placebo): Balance disorder and vomiting.
  - Golodirsen (incidence ≥ 20% and higher than placebo): Headache, pyrexia, fall, abdominal pain, nasopharyngitis, cough, vomiting, and nausea.
  - Viltolarsen (incidence ≥ 15%): Upper respiratory tract infection, injection site reaction, cough, and pyrexia.

DOSING AND ADMINISTRATION

Table 5. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Amondys 45 (casimersen)	Injection	IV infusion	Once weekly	Monitor renal function
Emflaza (deflazacort)	Tablets, suspension	Oral	Once daily	
Exondys 51 (eteplirsen)	Injection	IV infusion	Once weekly	
Vyondys 53 (golodirsen)	Injection	IV infusion	Once weekly	Monitor renal function
Viltepso (viltolarsen)	Injection	IV infusion	Once weekly	Monitor renal function

See the current prescribing information for full details

CONCLUSION

- DMD is a rare, genetic neuromuscular disease characterized by progressive loss of muscle function, resulting in early death due to respiratory or cardiac failure.
- No currently available therapies cure DMD or halt disease progression. Corticosteroids are the mainstay of pharmacologic therapy for DMD and may prolong ambulation and participation in activities of daily living.
- Emflaza (deflazacort) is the only corticosteroid indicated specifically for the treatment of DMD. Deflazacort is available as oral tablets or suspension and is administered once daily.
  - Other corticosteroids such as prednisone have been used off-label for decades to treat DMD. RCTs and clinical practice guidelines do not support the superiority of one corticosteroid over the others for DMD.
- The FDA granted biomarker-based accelerated approvals to 4 antisense oligonucleotides that demonstrated increases in dystrophin protein expression in muscle biopsy tissue. There is no consensus on the threshold of dystrophin expression in skeletal muscle fibers required to increase or to normalize muscle function in patients with DMD. The exon-skipping therapies are administered once weekly via IV infusion.
  - Amondys 45 (casimersen) is the only exon-skipping therapy indicated for DMD patients with mutations amenable to exon 45 skipping (approximately 8% of the DMD population).
  - Exondys 51 (eteplirsen) is the only exon-skipping therapy indicated for DMD patients with mutations amenable to exon 51 skipping (approximately 13% of the DMD population).
  - Vyondys 53 (golodirsen) and Viltepso (viltolarsen) are both indicated for DMD patients with mutations amenable to exon 53 skipping (approximately 9% of the DMD population).
- The clinical benefit of exon-skipping therapies has not been established and will be evaluated in ongoing confirmatory studies, which are expected to conclude between 2023 and 2026.

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