Therapeutic Class Overview
EXONDYS 51 (Agent for Duchenne Muscular Dystrophy [DMD])

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, 2016). 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, 2016).
    - 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, 2016). Absence of dystrophin leads to muscle damage, with replacement by fat and collagen (FDA Summary Review, 2016).
    - 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 (Exondys 51 Formulary Submission Dossier, 2016; 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, 2016; MDA Web site).
- DMD occurs in approximately 1 out of every 3500 to 5000 male infants worldwide (Exondys 51 Formulary Submission Dossier, 2016). While DMD primarily affects boys, in rare cases, female carriers can exhibit a wide range of clinical severity and may have comorbidities including muscle weakness, difficulty walking, and cardiac abnormalities (Exondys 51 Formulary Submission Dossier, 2016).
- Treatment for DMD has been largely supportive and utilizes glucocorticoids such as prednisone, which are widely believed to delay the loss of ambulation and respiratory decline by several years. Another glucocorticoid, which has been widely available outside of the United States for many years, Emflaza (deflazacort), recently garnered FDA approval for treatment of DMD (FDA Summary Review, 2016; Gloss et al, 2016; UpToDate, 2016[b]).
    - Although the time of steroid initiation in ambulatory boys with DMD varies by individual, most guidelines generally agree that glucocorticoids can be offered to patients ≥ 4 years of age whose motor skills have plateaued or are declining (Bushby et al, 2010; UpToDate, 2016[b]).
- On September 19, 2016, the FDA announced the approval of Sarepta Therapeutics' Exondys 51 (eteplirsen), an orphan drug for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. The FDA additionally granted eteplirsen priority review status, fast track status, and rare pediatric disease designation (FDA Web site; Sarepta Therapeutics News Release, 2016).
    - This indication received accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with eteplirsen.
    - A clinical benefit of eteplirsen has not been established and continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.
- Eteplirsen is a phosphorodiamidate morpholino oligomer (PMO) designed to target the pre-mRNA transcripts of the dystrophin gene so that exon 51 is excluded, or skipped, from the mature, spliced mRNA (FDA Summary Review, 2016). Theoretically, by restoring the mRNA reading frame, a truncated but nevertheless partially functional form of the dystrophin protein can be produced by muscle cells, thereby delaying disease progression.
    - Eteplirsen is specific for exon 51 mutations, a subset of the mutations that cause DMD in ~13% of the overall DMD patient population.
- Under accelerated approval provisions, an effect on a surrogate marker that is determined by the FDA to be reasonably likely to predict clinical benefit can support approval, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments (FDA Advisory Committee Meeting Minutes, 2016). An effect on an intermediate clinical endpoint (ie, a clinical endpoint that can be measured earlier than irreversible morbidity or mortality [IMM] and that is reasonably likely to predict an effect on IMM or other clinical benefit) can also serve as a basis for accelerated approval (FDA Advisory Committee Meeting Minutes, 2016).
    - In the case of eteplirsen, dystrophin production (measured by changes in the percentage of dystrophin-positive fibers assessed by immunohistochemistry [IHC] and/or by changes in the dystrophin protein levels

quantified by Western Blot) served as the primary surrogate endpoint in the clinical trials, while the change from baseline in the 6-minute walk test (6MWT) distance was the primary clinical outcome.

- Medispan Class: Muscular Dystrophy Agents

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
EXONDYS 51™ (eteplirsen)	Sarepta Therapeutics, Inc.	09/19/2016	-

(Drugs@FDA, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	EXONDYS 51 (eteplirsen) Sarepta Therapeutics, Inc.
• 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. o This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with eteplirsen. • A clinical benefit of eteplirsen has not been established. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.	✔

(EXONDYS 51 Prescribing Information, 2016)

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

CLINICAL EFFICACY SUMMARY

Clinical trials

- The clinical development program for eteplirsen (also referred to as AVI-4658) in male patients with DMD included the 2 early phase Studies 33 and 28, pivotal Phase 2b Study 201 and its extension Study 202, ongoing Phase 2 Studies 203 and 204 (both with no data yet available), and the ongoing, confirmatory Phase 3 PROMOVI Study (Study 301).
- Study 33 was a Phase 1/2, single-blind (SB), non-randomized, placebo-controlled (PC), dose-escalation, proof-of-concept, safety and efficacy study in 7 patients with varying degrees of ambulation and with deletions amenable to exon 51 skipping (Kinali et al, 2009).
    - Patients received a single intramuscular (IM) dose of eteplirsen (low-dose, 0.09 mg [n = 2]; high-dose, 0.9 mg [n = 5]) in the extensor digitorum brevis (EDB) muscle of one foot and an IM dose of normal saline placebo in the EDB muscle of the opposite foot.
    - Open biopsies of both EDB muscles were conducted 3 to 4 weeks following the injection to assess the safety and tolerability of eteplirsen (primary endpoint), as well as its biochemical efficacy (ie, its ability to restore dystrophin protein production by exon skipping) [secondary endpoint].
    - No adverse events (AEs) related to eteplirsen administration were reported.
    - Both patients who received low-dose eteplirsen showed little expression of dystrophin. IM injection of the higher dose resulted in increased dystrophin expression in all treated EDB muscles, although the immunostaining results were not uniform.

  - Review of Study 33 data by the FDA found that while an increase in dystrophin expression was reported adjacent to the needle track, it was not clear whether, or to what degree, this might reflect the activity of eteplirsen when given by the intravenous (IV) route, which does not produce similar high local concentrations or mechanical effects (FDA Briefing Document, 2016).
- Study 28 was a 12-week, Phase 1b/2a, open-label (OL), dose-escalation study conducted in 19 ambulatory patients with deletions amenable to exon 51 skipping (Cirak et al, 2011).
  - Patients were assigned to 6 cohorts that varied by dose (0.5 mg/kg, 1 mg/kg, 2 mg/kg, 4 mg/kg, 10 mg/kg, and 20 mg/kg) and received an IV infusion of eteplirsen once weekly for 12 weeks. The safety and tolerability of eteplirsen were the primary endpoints, while the biochemical efficacy and pharmacokinetic (PK) parameters of eteplirsen were the secondary endpoints.
  - Eteplirsen was well tolerated with no drug-related serious adverse events (SAEs).
  - Eteplirsen induced exon 51 skipping in all cohorts and new dystrophin protein expression in a significant dose-dependent ($p = 0.0203$), but variable manner in boys from cohort 3 (dose 2 mg/kg) and onwards.
  - Seven patients responded to treatment (1 patient in cohort 3 [2 mg/kg], 3 patients in cohort 5 [10 mg/kg], and 3 patients in cohort 6 [20 mg/kg]), in whom the mean dystrophin fluorescence intensity increased from 8.9% (95% confidence interval [CI]: 7.1 to 10.6) to 16.4% (95% CI: 10.8 to 22.0) of normal control after treatment ($p = 0.0287$).
  - The 3 patients with the greatest responses to treatment (1 each from cohorts 3, 5, and 6) had 21%, 15%, and 55% dystrophin-positive fibers after treatment and these findings were confirmed with Western blot, which showed an increase after treatment of protein levels from 2% to 18%, from 0.9% to 17%, and from 0% to 7.7% of normal muscle, respectively.
  - Review by the FDA found that the results of Study 28 did not appear to be interpretable due to concerns about the reliability of the methods and procedures used during the study (FDA Briefing Document 2016).
    - Western blot bands were too saturated to allow for the reliable quantification of dystrophin.
    - The sponsor reported that repeating and re-analysis of assays when unblinded to treatment may have increased the risk of bias and false positive findings.
- Study 201 was a 24-week, Phase 2b, double-blind (DB), PC, randomized controlled trial (RCT) in 12 ambulatory patients 7 to 13 years of age with deletions amenable to exon 51 skipping; all 12 patients rolled over into the ongoing, Phase 2, OL, multi-dose, long-term extension Study 202 for an additional 212 weeks. Data from these studies supported the eteplirsen new drug application (NDA); results were published by Mendell et al (2013).
  - Patients were randomized 1:1:1 to receive once weekly IV infusions of eteplirsen 30 mg/kg/week (n = 4), 50 mg/kg/week (n = 4), or placebo (n = 4) (ie, Cohorts 1, 2, and 3, respectively) for the first 24 weeks.
  - During Weeks 25 to 28, the 4 patients originally treated with placebo were switched to the eteplirsen 30 mg/kg or 50 mg/kg groups (n = 2 in each group); patients remained on these doses throughout the OL extension study. All patients underwent biceps biopsies at baseline and deltoid biopsies at Week 48 for analysis of the percentage of dystrophin-positive fibers assessed by immunohistochemistry (IHC) (surrogate endpoint). Additional biceps biopsies were obtained at Week 12 (from 4 patients in Cohort 2 and 2 patients in Cohort 3) or Week 24 (from 4 patients in Cohort 1 and 2 patients in Cohort 3). The 6MWT was the primary functional outcome measure and was performed pre-treatment and post-treatment through Week 48 (every 4 weeks through Week 36; then at Week 48).
  - Once weekly treatment with eteplirsen 30 mg/kg for 24 weeks resulted in a 22.9% (range: 15.9% to 29%) mean increase in dystrophin-positive fibers from baseline compared to the combined placebo group ($p \leq 0.002$). Once weekly treatment with eteplirsen 50 mg/kg for 12 weeks did not result in an increase of dystrophin-positive fibers compared to baseline and was not statistically different compared to the placebo groups. The within-cohort comparison of the percentage of dystrophin-positive fibers (Week 24 vs. baseline for the 30 mg/kg group and Week 12 vs. baseline for the 50 mg/kg group) resulted in a statistically significant difference for the 30 mg/kg group ($p \leq 0.004$), but not for the 50 mg/kg group, or the combined placebo groups.
  - At Week 48, the 30 and 50 mg/kg groups showed statistically significant ($p \leq 0.001$) increases in the percentage of dystrophin-positive fibers (mean = 47.3%, range = 29.8% to 60.3%).
  - The adjusted mean changes for the 6MWT distance from baseline to Week 24 were as follows: placebo: -25.8 m (± 30.6 m); 30 mg/kg: -128.2 m (± 31.6 m); and 50 mg/kg: -0.3 m (± 31.2 m).
  - Adjusted mean changes from baseline to Week 48 on the 6MWT distances were the following: placebo/delayed group: -68.4 m (± 37.6 m); 30 mg/kg: -153.4 m (± 38.7 m); and 50 mg/kg: +21 m (± 38.2 m).

- In a post hoc analysis by Mendell et al (2016), the disease progression of the 12 eteplirsen-treated patients originally recruited for Studies 201 and 202 was compared to 13 external controls that were matched on exon 51 skipping genotype, age, corticosteroid use, and the existence of sufficient longitudinal data to allow for the identification of baseline and follow-up visits.
    - Eteplirsen-treated patients demonstrated a statistically significant advantage of 151 m ($p < 0.01$) on the 6MWT and experienced a lower incidence of loss of ambulation in comparison to matched historical controls amenable to exon 51 skipping. The authors concluded that over 3 years of follow-up, eteplirsen-treated patients showed a slower rate of decline in ambulation assessed by the 6MWT compared to untreated matched historical controls.
- FDA review of the entirety of data captured from Studies 201 and 202 identified several technical and operational issues, alongside methodological flaws in study design that cast doubt on the reliability and interpretation of the results (FDA Briefing Document, 2016; FDA Summary Review, 2016).
    - The original data from Nationwide Children's Hospital submitted to the FDA showed that immunostaining for dystrophin appeared to increase markedly in all groups with time, with some 50 to 60% of fibers staining positive for dystrophin at 48 weeks. The results of an FDA-recommended re-analysis with independent masked readers failed to show a significant increase in dystrophin-positive fiber counts in eteplirsen-treated patients. Results at Week 180 in the blinded re-analysis showed an increase of only 17%.
        - Analyses based on IHC can overestimate the amount of dystrophin in tissue sections because a muscle fiber can be considered "positive" if it exhibits any staining at all, even if the level of dystrophin is very low.
        - The publication by Mendell et al (2013) that claimed a remarkable treatment effect was therefore considered to be misleading and the FDA has since called for its retraction.
    - Western blot analyses, required by the protocol and used to more accurately quantify dystrophin levels, were confounded by comparisons of biopsied tissue from different muscles at baseline (biceps) and at Weeks 48 and 180 (deltoid). Archived pre-treatment muscle biopsy samples were available for re-analysis from only 3 patients in Studies 201/202; additional samples were obtained from 6 patients, selected externally. Biopsy samples from controls were also obtained from different muscle groups than the eteplirsen-treated patients. For these reasons, the control value of 0.08% dystrophin in untreated patients was considered uncertain, making the relative change in dystrophin difficult to estimate.
    - Contrary to the Mendell et al (2016) post hoc analysis, the FDA found that the clinical course of eteplirsen patients over more than 3.5 years of treatment with eteplirsen had been generally similar to the expected natural history of patients provided with intensive supportive care.
- Study 203 is an ongoing, 96-week, Phase 2, OL, SB, non-randomized study in ambulatory patients aged 4 to 6 years with DMD and deletions amenable to exon 51 skipping (estimated enrollment N = 40) (ClinicalTrials.gov Web site). Twenty patients in the treatment arm will receive eteplirsen IV 30 mg/kg once weekly and an untreated group of 20 patients with deletions not amenable to exon 51 skipping will serve as controls. The number of patients with treatment-emergent adverse events (TEAEs) is the primary outcome, while the change from baseline in the percentage of dystrophin-positive skeletal muscle fibers is the secondary outcome.
- Study 204 is an ongoing, 96-week, Phase 2, OL, single-arm, safety study in patients aged 7 to 21 years with advanced DMD (ie, non-ambulatory or incapable of walking ≥ 300 m on the 6MWT) and deletions amenable to exon 51 skipping (estimated enrollment N = 20) (ClinicalTrials.gov Web site). All patients will receive eteplirsen 30 mg/kg IV once weekly. The number of patients with TEAEs is the primary outcome. Clinical laboratory or vital sign/electrocardiogram (ECG) abnormalities and changes in pulmonary function tests are among the secondary outcome measures.
- Study 301 [PROMOVI] is an ongoing, 96-week, Phase 3, OL, multi-center (MC) confirmatory study whose objective is to provide evidence of efficacy for eteplirsen in ambulatory DMD patients 7 to 16 years of age with deletions amenable to exon 51 skipping (ClinicalTrials.gov Web site; Exondys 51 Formulary Submission Dossier, 2016; FDA Summary Review, 2016). The estimated enrollment is 160 patients, 80 of whom will receive eteplirsen 30 mg/kg IV once weekly, while the remaining 80 patients with deletions not amenable to exon 51 skipping will be recruited to the untreated group. All patients will receive 1 biopsy at baseline and then will be randomized to receive a second muscle biopsy at either Weeks 24, 48, 72, or 96. The change from baseline in the 6MWT distance is the primary endpoint, while dystrophin levels assessed by Western blot and the percentage of dystrophin-positive fibers assessed by IHC are among the key secondary endpoints.

  - In order to gain additional information that might provide evidence of an effect on a surrogate marker that was reasonably likely to predict clinical benefit, the FDA requested an interim analysis of a subset of samples.
  - At the time of this request, 13 patients (mean age of 8.9 years) had been treated with OL eteplirsen for 48 weeks and had a muscle biopsy at baseline and after 48 weeks of treatment. An FDA inspection team observed the performance of the Western blot assays and considered the results to be reliable.
  - Of the 12 patients with evaluable results, 8 (two-thirds) had a change of 0.25% or less; only 1 patient (8%) had a change > 1%. The sponsor used 3 methods to consider the numerous values below the limit of quantification, but irrespective of the method used, the mean treatment effect was similar, ranging from 0.22% to 0.32% of normal, a change of approximately 2 to 3 parts per thousand that was nevertheless statistically significant ($p < 0.05$).
  - At the FDA, members of the review team disagreed on whether the increase in dystrophin production observed in eteplirsen-treated patients would be reasonably likely to predict a clinical benefit (FDA Summary Review, 2016).
- In a decisional memo dated July 14, 2016, the Director for the Center for Drug Evaluation and Research (CDER) concluded that the data submitted met the standard for accelerated approval based on the surrogate endpoint of increased dystrophin protein production, which she believed was reasonably likely to predict a clinical benefit. An appeal of this decision from the Director of the Office of Drug Evaluation I (ODE-1) convened the Agency Scientific Dispute Process Review Board, whose Chair ultimately agreed with the conclusions of the ODE-1 Director against accelerated approval. On September 16, 2016, the FDA Commissioner set forth a final decision that deferred to the CDER Director's judgment and authority to make the decision to approve eteplirsen under the accelerated approval pathway. The FDA has additionally called for the retraction of Mendell et al (2013), a publication that numerous officials claim is based on unreliable assay measures which greatly overstated the degree of dystrophin protein expression, thereby leading to unrealistic expectations and hope for DMD patients and their families.
- Due to the number of methodological flaws and limitations in study designs of the eteplirsen pivotal trials, final approval of eteplirsen for DMD in patients with deletions amenable to exon 51 skipping was based on the following data permitted by the FDA and detailed in the product's prescribing information:
  - Studies 201 and 202: The average dystrophin protein level after 180 weeks of treatment with eteplirsen was 0.93% of the dystrophin level in healthy subjects. There was no significant difference in change in the 6MWT distance between patients treated with eteplirsen and those treated with placebo in Study 201. Study 202 failed to provide evidence of a clinical benefit of eteplirsen compared to the external control group.
  - Confirmatory Phase 3 Study 301 [PROMOVI]: In the 12 patients with evaluable results, the pre-treatment dystrophin level was 0.16% ± 0.12% (mean ± standard deviation [SD]) of the dystrophin level in a healthy subject and 0.44% ± 0.43% after 48 weeks of treatment with eteplirsen ($p < 0.05$). The median increase after 48 weeks was 0.1%.

Treatment Guidelines

- Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management (Bushby et al, 2010):
  - Diagnosis should be done by a neuromuscular specialist who can assess the child clinically and can rapidly access and interpret appropriate investigations in the context of the clinical presentation.
  - Suspicion of the diagnosis of DMD should be considered irrespective of family history and is usually triggered in 1 of 3 ways: (1) most commonly, the observation of abnormal muscle function in a male child; (2) the detection of an increase in serum creatine kinase tested for unrelated indications; or (3) after the discovery of increased transaminases (aspartate aminotransferase and alanine aminotransferase, which are produced by muscle as well as liver cells).
  - Initial symptoms might include delayed walking, frequent falls, or difficulty with running and climbing stairs. Although DMD is typically diagnosed at around 5 years of age, the diagnosis might be suspected much earlier because of delays in attainment of developmental milestones, such as independent walking or language.
  - The key tests done on the muscle biopsy for DMD are immunocytochemistry and immunoblotting for dystrophin, and should be interpreted by an experienced neuromuscular pathologist. A muscle biopsy can provide information on the amount and molecular size of dystrophin, as long as the protein is present. Differentiating total and partial absence of dystrophin can help to distinguish DMD from a milder dystrophinopathy phenotype. Electron microscopy is not required to confirm DMD. Genetic testing after a

positive biopsy diagnosis of DMD is mandatory. A muscle biopsy is not necessary if a genetic diagnosis is secured first, particularly as some families might view the procedure as traumatic.
    - The genetic tests commonly used to identify dystrophin mutations are multiplex PCR, multiplex ligation-dependent probe amplification, single-condition amplification/internal primer, and multiplex amplifiable probe hybridization. Multiplex PCR is widely available and the least expensive, but only detects deletions and does not cover the whole gene, so that a deletion might not always be fully characterized. Multiplex ligation-dependent probe amplification and amplifiable probe hybridization will detect deletions and duplications and cover all exons, and single-condition amplification/internal primer will detect deletions and provide sequence data. None of these techniques is universally available.
    - Glucocorticoids are the only medication currently available that slows 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 side-effects. 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 side-effects) 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.
- 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 loss of ambulation 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

- EXONDYS 51 has no contraindications or warnings and precautions. The most common adverse reactions were balance disorder and vomiting.

Table 3. Adverse reactions in DMD patients treated with eteplirsen 30 or 50* mg/kg/week with an incidence at least 25% more than placebo in Study 201 (ie, Study 1)

Adverse reactions	Eteplirsen (n = 8)	Placebo (n = 4)
Balance disorder	38%	0%
Vomiting	38%	0%
Contact dermatitis	25%	0%

* 50 mg/kg/week = 1.7 times the recommended dosage

(EXONDYS 51 Prescribing Information, 2016)

- In the 88 patients who received ≥ 30 mg/kg/week of eteplirsen for up to 208 weeks in clinical studies (201/202, 203, 204, and 301), the following events were reported in ≥ 10% of patients and occurred more frequently than on the same dose in Study 1: vomiting, contusion, excoriation, arthralgia, rash, catheter site pain, and upper respiratory tract infection.
- There have been reports of transient erythema, facial flushing, and elevated temperature occurring on the days of eteplirsen infusion.
- Risk Assessment and Medical Reviews by the FDA (2016) reported the following:
    - No patients died during the eteplirsen clinical development program.
    - Nonfatal SAEs were reported in 6 patients in the safety population. The SAEs included wound infection, vomiting, ankle fracture, femur fracture, decreased oxygen saturation, and viral lymphadenitis. These events were considered by the clinical reviewers as unrelated to treatment.
    - Nine AEs occurring in 6 patients were assessed as severe. The events included incision site hemorrhage, hemorrhoids, back pain, nasal congestion, bone pain, loss of balance, viral lymphadenitis, femur fracture, and cardiomyopathy with left ventricular dysfunction. All of the events were judged by the investigator and clinical reviewers to be unrelated except for cardiomyopathy, which was considered by the investigator as possibly related; a review of echocardiograms for this patient, a 10-year-old boy, showed that he had pre-existing cardiomyopathy. The boy discontinued treatment due to a decrease in left ventricular ejection fraction after having received 7 once-weekly doses of eteplirsen 4 mg/kg.
    - As the placebo-controlled experience is extremely limited for eteplirsen (ie, 8 patients on drug vs. 4 patients on placebo treated for 24 weeks in Study 201), most of the safety experience comes from OL studies, which greatly limits the interpretability of data, in particular considering the various events and complications that are expected as DMD progresses.
    - In Studies 201/202, which have been ongoing for nearly 4 years, with most of the experience without a concurrent control, the clinical reviewer describes that infections were noted, including an increase in respiratory infections, which is expected in that population. The clinical reviewer also noted some AEs related to neuromuscular symptoms and hypersensitivity-related events in the later part of these studies.
    - In the other OL trials, AEs expected in the DMD population were observed, and the lack of a concurrent control makes it impossible to determine whether their incidence was increased by eteplirsen treatment.
    - Various laboratory test changes of unclear clinical significance in eteplirsen-treated patients were described, but no changes of clinical relevance in vital signs or ECGs were noted by the clinical reviewer.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Usual Recommended Dose	Administration Considerations
EXONDYS 51 (eteplirsen)	Injection: IV	30 mg/kg once weekly	Infuse over 35 to 60 minutes; application of a topical anesthetic cream to the infusion site prior to administration may be considered

(EXONDYS 51 Prescribing Information, 2016)

SPECIAL POPULATIONS

Table 5. Special Populations

Drug	Population and Precaution			
	Elderly	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
EXONDYS 51 (eteplirsen)	As DMD is largely a disease of children and young adults, there is no geriatric experience with EXONDYS 51.	Not studied	Not studied	No human or animal data are available to assess the use of EXONDYS 51 during pregnancy or its effects on milk production, on breastfed infants, or the presence of eteplirsen in milk.

(EXONDYS 51 Prescribing Information, 2016)

CONCLUSION

- EXONDYS 51 (eteplirsen) is an orphan drug indicated for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. The FDA granted eteplirsen priority review status, fast track status, and rare pediatric disease designation (FDA Web site; Sarepta Therapeutics News Release, 2016).
    - This indication received accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with eteplirsen.
    - A clinical benefit of eteplirsen has not been established and continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.
- Eteplirsen is a phosphorodiamidate morpholino oligomer (PMO) designed to target the pre-mRNA transcripts of the dystrophin gene so that exon 51 is excluded, or skipped, from the mature, spliced mRNA (FDA Summary Review, 2016). Theoretically, by restoring the mRNA reading frame, a truncated but nevertheless partially functional form of the dystrophin protein can be produced by muscle cells, thereby delaying disease progression.
    - Eteplirsen is specific for exon 51 mutations, a subset of the mutations that cause DMD in ~13% of the overall DMD patient population.
- The clinical development program for eteplirsen in male patients with DMD included the 2 early phase Studies 33 and 28, pivotal Phase 2b Study 201 and its extension Study 202, ongoing Phase 2 Studies 203 and 204, and the ongoing, confirmatory Phase 3 PROMOVI Study (Study 301). Serious methodological flaws in the study design of the pivotal studies led to the exclusion of the majority of data from studies 201 and 202 published by Mendell et al (2013) from the final text of the EXONDYS 51 prescribing information. Results from Studies 201, 202, and 301 that were permitted by the FDA included the following:
    - Studies 201/202 (N = 12): The average dystrophin protein level after 180 weeks of treatment with eteplirsen was 0.93% of the dystrophin level in healthy subjects. No significant changes in the 6MWD were noted.
    - Study 301 (N = 12 evaluable patients): The pre-treatment dystrophin level was 0.16% ± 0.12% (mean ± standard deviation) of the dystrophin level in a healthy subject and 0.44% ± 0.43% after 48 weeks of treatment with eteplirsen ($p < 0.05$). The median increase after 48 weeks was 0.1%.
- The most common adverse reactions with eteplirsen (incidence ≥ 35% and higher than placebo) with eteplirsen use in Studies 201 and 202 were balance disorder (38%) and vomiting (38%).
- The recommended dose of eteplirsen is 30 mg/kg administered as a 35- to 60-minute IV infusion once weekly. Application of a topical anesthetic cream to the infusion site may be considered prior to administration of eteplirsen.
- While the approval of eteplirsen for patients with DMD amenable to exon 51 skipping was an historic milestone for patients and their families, serious methodological flaws in study design brought to light during the FDA review have called into question the ability of eteplirsen to produce dystrophin in high enough amounts that may be reasonably likely to produce a clinical benefit.

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