

**POLICY:** Muscular Dystrophy – Exondys 51™ (eteplirsen intravenous infusion – Sarepta)

**APPROVAL DATE:** 04/10/2019

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## OVERVIEW

Exondys 51 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.<sup>1</sup> Exondys 51 was approved for this indication under accelerated approval based on an increase in dystrophin observed in the skeletal muscle of some patients who received the drug. However, a clinical benefit of Exondys has not been established. The prescribing information notes that continued FDA-approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

## Disease Overview

DMD is an X-linked recessive disease affecting 1 in 3,600 to 6,000 newborn male infants.<sup>2</sup> The disease is attributed to large frame-shift deletions in the DMD gene (chromosome Xp21) which lead to loss of a structural protein of muscle cells (dystrophin).<sup>3</sup> Over 4,700 mutations on the DMD gene have been identified which lead to a deficiency in production of dystrophin.<sup>2</sup> Therefore, the type of mutation and its effect on the production of dystrophin accounts for the variable phenotypic expression.<sup>4</sup> Females carriers are usually asymptomatic but some may show mild symptoms.<sup>2</sup> There are wide variances in how quickly DMD progresses, but without intervention death is at approximately 19 years of age.<sup>2-4</sup> With respiratory, cardiac, orthopedic and rehabilitative interventions and use of corticosteroids, children born today can have a life expectancy of up to 40 years.

Exondys 51 is an antisense oligonucleotide designed to bind to exon 51 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 51 skipping.<sup>1</sup> These patients represent approximately 13% of all patients with DMD.<sup>5</sup> This genetic manipulation intends to restore the reading frame of the resulting mRNA. The result would be production of a shortened, but partially functional dystrophin protein as seen in less severe forms of muscular dystrophy (e.g., Becker muscular dystrophy).

## Guidelines

There are guidelines for the diagnosis and management of DMD available from the DMD Care Considerations Working Group (2018).<sup>4</sup> Genetic testing for a DMD mutation in a blood sample is always required. By fully characterizing the mutation, the predicted effect on the reading frame can be identified, which is the major determinant of phenotype and will determine eligibility for mutation-specific clinical trials. In patients with no mutation identified but with signs/symptoms of DMD, a muscle biopsy is clinically indicated. Glucocorticoids slow decline in muscle strength and function in DMD. Use of corticosteroids reduces the risk of scoliosis and stabilizes pulmonary function. Continued treatment after the patient loses ambulation provides a reduction in the risk of progressive scoliosis and stabilization of pulmonary function tests. Therefore, glucocorticoids should be considered for all patients with DMD. Exondys 51 is mentioned as an emerging product, approved by an accelerated pathway for those with a mutation in the dystrophin gene amenable to exon 51 skipping.

## **POLICY STATEMENT**

The prescribing information for Exondys 51 states that a clinical benefit has not been established. Due to the lack of clinical efficacy data, **approval is not recommended** for Exondys 51.

**Automation:** None.

## **RECOMMENDED AUTHORIZATION CRITERIA**

None.

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## **CONDITIONS NOT RECOMMENDED FOR APPROVAL**

Exondys 51 has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

- 1. Duchenne Muscular Dystrophy (DMD).** Due to the lack of clinical efficacy data, approval is not recommended for Exondys 51. The prescribing information for Exondys 51 states that a clinical benefit has not been established.<sup>1</sup> Furthermore, a systemic review and meta-analysis does not show benefit of exon-skipping therapies for DMD.<sup>10</sup> FDA has required a randomized, controlled trial evaluation post-marketing to establish efficacy of Exondys 51. Results are expected in 2021.

The efficacy of Exondys 51 was evaluated in open-label studies in patients with DMD that is amenable to exon 51 skipping.<sup>1,6-9</sup> One study (n = 12) assessed the effect of Exondys 51 on dystrophin and the potential clinical benefit; however, there was insufficient information on dystrophin levels prior to treatment so it is not possible to estimate a treatment effect on dystrophin levels. The adjusted mean change in the 6-minute walk test (6MWT) from baseline to Week 24 was -25.8 (±30.6) meters for placebo; -128.2 (±31.6) meters for Exondys 51, 30 mg/kg; and -0.3 (±31.2) meters for Exondys 51, 50 mg/kg. An extension of this study evaluated the same patients and compared disease progression with matched historical controls; at Month 36 the difference in 6MWT distance for Exondys 51 vs. historical control was 121 meters in favor of the Exondys 51 cohort (P = 0.028). Over 36 months, ambulation was lost in 16.7% of patients (n = 2/12) treated with Exondys 51 vs. 46.2% of patients (n = 6/13) in the historical control cohort. The average dystrophin protein level after 180 weeks of treatment with Exondys 51 was 0.93% of the dystrophin level in healthy subjects. But because there was insufficient information on baseline dystrophin levels prior to treatment, it is not possible to estimate a treatment effect. Following 240 weeks of treatment, the percent predicted forced vital capacity (FVC%p) was a decrease of 2.3% per year with Exondys 51 compared with a decrease of 4.1% in a natural history cohort.<sup>11</sup> In patients treated with Exondys 51, the percent predicted maximum inspiratory pressure (MIP%p) decreased by 1% per year, and the percent predicted maximum expiratory pressure (MEP%p) decreased by 2.6% per year. However, MIP and MEP were not assessed in the natural history cohort. Another study included 12 new patients with DMD and reports only on the effect of Exondys 51 on dystrophin levels; further clinical efficacy data are not yet available for these 12 patients.<sup>7-9</sup> After 48 weeks of treatment with Exondys 51 the dystrophin level was 0.44% ± 0.43% of the dystrophin level in healthy subjects (P < 0.05). The median increase after 48 weeks was 0.1%.

- Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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## HISTORY

| Type of Revision | Summary of Changes* | Approval Date |
|------------------|---------------------|---------------|
| New Policy       | --                  | 04/10/2019    |