VENTURA COUNTY
HEALTH CARE PLAN

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Muscular Dystrophy – Exondys 51 Utilization Management Medical Policy
- Exondys 51™ (eteplirsen intravenous infusion – Sarepta)

REVIEW DATE: 04/27/2022

OVERVIEW

Exondys 51, an antisense oligonucleotide, 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.[1] 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.[2] 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).[3] 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.[1] These patients represent approximately 13% of all patients with DMD.[5]

Guidelines

There are guidelines for the diagnosis and management of DMD available from the DMD Care Considerations Working Group (2018).[4] 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

Due to the lack of clinical efficacy data, **approval is not recommended** for Exondys 51.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

None.

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.[1] Furthermore, a systematic review and meta-analysis does not show benefit of exon-skipping therapies for DMD.[10] FDA has required a randomized, controlled trial evaluation post-marketing to establish efficacy of Exondys 51. The anticipated study completion is February 2026.[13]

   The efficacy of Exondys 51 was evaluated in open-label studies in patients with DMD that is amenable to exon 51 skipping.[1,6-9,11] 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.[11] 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.[7-9] 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%.

   The PROMOVI trial was a Phase III, multicenter, open-label, non-randomized trial evaluating the efficacy and safety of Exondys 51 in patients 7 to 16 years of age with DMD and genetic deletions amenable to exon 51 skipping (n = 79).[12] At Week 96, mean 6MWT distance and mean FVC%p decreased from baseline. The results were consistent with Phase II trials of Exondys 51. Several study limitations including the open-label design with lack of a placebo-control group, lack of a prospective, mutation-matched untreated control arm, lack of data on treatment effects in patients earlier in the disease course were not addressed.

2. 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	Review Date
Annual Revision	No criteria changes.	04/21/2021
Annual Revision	No criteria changes.	04/27/2022