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: 04/15/2026

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 51 has not been established. The prescribing information notes that continued FDA-approval for this indication may be contingent upon verification 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).** Approval is not recommended due to the unclear clinical benefit of Exondys 51 and lack of clinical efficacy data. Shortcomings of the clinical data with Exondys 51 are numerous. In the pivotal trials, an increase in dystrophin was observed in a very limited number of patients treated with Exondys 51 and the significance of the increase could not be correlated with clinical benefit. Further, the increase in dystrophin was limited by methodological shortcomings which cast doubt on the reliability of biopsies taken during the first 48 weeks of the pivotal trials. Additional limitations of the data include that the pivotal trials only evaluated Exondys 51 in ambulatory patients; therefore, it is unknown if patients with more advanced disease and greater muscle deterioration would derive any benefit from treatment. There is inadequate information available to determine if Exondys 51 provides a benefit regarding cardiac and respiratory complications which greatly contribute to the morbidity and mortality of patients with DMD. Exondys 51 has not been proven to alter or delay disease progression in patients with DMD amenable to exon 51 skipping. 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 October 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.

REFERENCES

1. Exondys 51™ intravenous infusion [prescribing information]. Cambridge, MA: Sarepta Therapeutics; December 2024.
2. Annexstad EJ, Lund-Petersen I, Rasmussen M. Duchenne muscular dystrophy. *Tidsskr Nor Laegeforen*. 2014;134(14):1361-1364.
3. Wood MJA. To skip or not to skip: that is the question for Duchenne muscular dystrophy. *Mol Ther*. 2013;21(12):2131-2132.
4. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. *Lancet Neurol.* 2018;17(3):251-267.
5. Flanigan KM, Voit T, Rosales XQ, et al. Pharmacokinetics and safety of single doses of drisapersen in non-ambulant subjects with Duchenne muscular dystrophy: results of a double-blind randomized clinical trial. *Neuromuscul Disord*. 2014;24(1):16-24.
6. Mendell JR, Rodino-Klapac LR, Sahenk Z, et al. Eteplirsen for the treatment of Duchenne muscular dystrophy. *Ann Neurol*. 2013;74(5):637-647.
7. FDA briefing document for the Peripheral and Central Nervous System Drugs Advisory Committee Meeting. Eteplirsen (NDA 206488). April 25, 2016. Data on file.
8. Mendell JR, Goemans N, Lowes LP, et al. Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy. *Ann Neurol.* 2016;79(2):257-271.
9. Peripheral and Central Nervous System Drugs Advisory Committee. Eteplirsen. April 25, 2016. Data on file.
10. Shimizu-Motohashi Y, Murakami T, Kimura E, et al. Exon skipping for Duchenne muscular dystrophy: a systematic review and meta-analysis. *Orphanet J Rare Dis*. 2018;13(1):93.
11. Kinane TB, Mayer OH, Duda PW, et al. Long-term pulmonary function in Duchenne muscular dystrophy: comparison of eteplirsen-treated patients to natural history. *J Neuromuscul Dis*. 2018;5(1):47-58.
12. McDonald CM, Sheih PB, Abel-Hamid HZ, et al; on behalf of the Italian DMD Telethon Registry Study Group, Leuven NMRC Registry Investigators, CINRG Duchenne Natural History Investigators, and PROMOVI Trial Clinical Investigators. Open-label evaluation of eteplirsen in patients with Duchenne muscular dystrophy amenable to exon skipping: PROMOVI trial. *J Neuromuscul Dis.* 2021;8:989-1001.
13. Sarepta Therapeutics. A study to compare safety and efficacy of a high dose of eteplirsen in participants with Duchenne muscular dystrophy (DMD) (MIS51ON). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2026 April 8]. Available at: https://clinicaltrials.gov/ct2/show/NCT03992430?term=NCT03992430&draw=2&rank=1. NLM Identifier: NCT03992430.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	05/15/2024
Annual Revision	No criteria changes.	04/30/2025
Annual Revision	No criteria changes.	04/15/2026