Drug Coverage Policy

Effective Date.....8/15/2024
Coverage Policy Number..... IP0135
Policy Title.....Exondys 51

Muscular Dystrophy – Exondys 51

- Exondys 51™ (eteplirsen intravenous infusion – Sarepta)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Cigna Healthcare Coverage Policy

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 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 leads to a loss of the 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.

Medical Necessity Criteria

Exondys 51 is considered medically necessary when the following are met:

FDA-Approved Indication

1. **Duchenne Muscular Dystrophy.** Approve for the duration noted if the patient meets ONE of the following (A or B):
    - **A.** Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, and v):
        - **i.** Less than 14 years of age at start of therapy; AND
        - **ii.** Documented diagnosis of Duchenne muscular dystrophy is confirmed by a pathogenic or likely pathogenic variant in the *DMD* gene that is amenable to exon 51 skipping; AND
        - **iii.** Able to walk a distance of at least 180 meters independently over 6 minutes; AND
        - **iv.** Medication is prescribed by, or in consultation with, a neurologist, neuromuscular specialist, or by a Muscular Dystrophy Association clinic.
    - **B.** Patient is Currently Receiving Exondys 51. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):
        - **i.** The above criteria were met prior to initiation of Exondys 51; AND
        - **ii.** Patient has experienced a beneficial clinical response, including the continued ability to walk; AND
        - **iii.** Medication continues to be prescribed by, or in consultation with, a neurologist, neuromuscular specialist, or by a Muscular Dystrophy Association clinic.

    Dosing. Approve 30 milligrams per kilogram administered once weekly as a 35 to 60-minute intravenous infusion

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Concurrent Use with Other Exon-skipping DMD Agents** (for example, Amondys 45, Viltepso, Vyondys 53). Currently, there is no clinical evidence to support concurrent use of exon-skipping agents for the treatment of DMD.

Coding Information

1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J1428	Injection, eteplirsen, 10 mg

References

1. Exondys 51™ intravenous infusion [prescribing information]. Cambridge, MA: Sarepta Therapeutics; January 2022.
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 2023 April 26]. Available at: https://clinicaltrials.gov/ct2/show/NCT03992430?term=NCT03992430&draw=2&rank=1. NLM Identifier: NCT03992430.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	Updated policy title; previously it was Eteplirsen. Added dosing to the policy.	8/15/2024

The policy effective date is in force until updated or retired.