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. 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.

Coverage Policy

Eteplirsen (Exondys 51™) is considered medically necessary when ALL of the following criteria are met:

- Documented diagnosis of Duchenne muscular dystrophy (DMD)
- Confirmed mutation of the DMD gene that is amenable to exon 51 skipping
- Individual is able to walk

Initial authorization is up to 6 months.

Eteplirsen (Exondys 51) is considered medically necessary for continued use when the initial criteria are met.

Reauthorization for up to 12 months.

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.

Eteplirsen (Exondys 51) is considered experimental, investigational or unproven for ANY other use.

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.
Please refer to the applicable benefit plan document to determine terms, conditions and limitations of coverage.

## FDA Approved Indications

**FDA Approved Indication**

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. This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with Exondys 51 [see Clinical Studies (14)]. A clinical benefit of Exondys 51 has not been established. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

## Recommended Dosing

**FDA Recommended Dosing**

The recommended dose of Exondys 51 is 30 milligrams per kilogram administered once weekly as a 35 to 60 minute intravenous infusion.

If a dose of Exondys 51 is missed, it may be administered as soon as possible after the scheduled time.

**Drug Availability**

Exondys 51 injection is supplied in single-dose vials. The solution is clear and colorless, and may have some opalescence.

- Single-dose vials containing 100 mg/2 mL (50 mg/mL) eteplirsen
- Single-dose vials containing 500 mg/10 mL (50 mg/mL) eteplirsen

## General Background

**Pharmacology**

Specific deletion mutations of the DMD gene result in termination of dystrophin protein translation by closing the reading frame prematurely. (Kinali, 2009) Closing the reading frame prematurely results in a truncated and nonviable dystrophin protein. Dystrophin is important for proper muscular function. (Yiu, 2015) Eteplirsen is an antisense oligonucleotide that binds to exon 51 of dystrophin pre-mRNA. Exon 51 is skipped during dystrophin protein translation when bound by eteplirsen. (Kinali, 2009) Reading frames in mutations where exons 45-50, 47-50, 48-50, 49-50, 50, 52, or 52-63 are deleted in the DMD gene may remain open during translation if exon 51 is bound by eteplirsen. (Kinial, 2009; Mendell, 2013) Skipping exon 51 in these specific mutations results in production of a truncated but viable dystrophin protein. (Kinali, 2009) Deletion mutations that may respond to exon 51 skipping account for approximately 13% of all DMD mutations. (CDER, 2016; Kinali, 2009)

**Professional Societies/Organizations**

American Academy of Neurology (2016) and the DMD Care Considerations Working Group (2010), which was selected by the Centers for Disease Control and Prevention state additional care for DMD is primarily supportive (e.g., physical therapy, exercise therapy, respiratory therapy, nutritional, psychosocial). (Bushby, 2010b) Dietary supplements are not endorsed by the panel but are used by many patients. Close cardiac monitoring is recommended in DMD patients. Cardiomyopathy and arrhythmias are common in DMD. Use of medications for heart failure may be appropriate when cardiomyopathy is identified. Follow current heart failure guidelines when heart failure is identified in a DMD patient. Various surgical techniques have also been used to help limit the effects of the disease (e.g., spinal fusion). (Bushby, 2010b) Guidelines do not specifically discuss the role of eteplirsen therapy in DMD. (Bushby, 2010a; Bushby 2010b; Gloss, 2016)

The American Board of Internal Medicine’s (ABIM) Foundation Choosing Wisely® Initiative:

No recommendations are available for eteplirsen (Exondys 51).

Centers for Medicare & Medicaid Services - National Coverage Determinations (NCDs)
There are no CMS National Coverage Determinations for eteplirsen (Exondys 51).

Clinical Efficacy

FDA Approved Indications

Two pivotal published trials evaluated eteplirsen for the treatment of DMD in 12 ambulatory, (i.e., able to walk 200 to 400 m on the 6MWT) pediatric male patients. (Mendell, 2013; Mendell, 2016) In the group who received the labeled dose, eteplirsen 30 mg/kg/week, there was a significant increase in dystrophin-positive fibers from baseline (22.9%; SE = 2.9%) compared with placebo (-4%; SE = 2.92%) at week 24 (P ≤ 0.002). No difference in dystrophin-positive muscle fibers from baseline was identified in the eteplirsen 50 mg/kg/week group (0.8%; SE = 3.55%) compared with placebo at week 12 (-4%; SE = 2.92%). Significant increases were also identified at week 48 in the eteplirsen 30 mg/kg/week (51.7%; SE = 3.54%; P ≤ 0.001) and eteplirsen 50 mg/kg/week (42.9%; SE = 6.72%; P ≤ 0.008) groups compared with placebo (-4%; SE = 2.92%). The adjusted mean change in 6 minute walk test (6MWT) from baseline for the eteplirsen 30 mg/kg/week group declined by 128.2 m ± 31.6 m at week 24 (no statistical comparison reported). Two patients in this group lost complete ambulation. The adjusted mean change in 6MWT from baseline increased to 14.2 m ± 14.4 m when these patients were removed from analysis (P = NS compared with placebo). There are ongoing trials assessing the clinical benefit of eteplirsen. Treatment will continue to week 144 to evaluate the long term effects of eteplirsen. The manufacturer, Sarepta Therapeutics, Inc. has indicated results are expected by the end of 2019.

Off Label Uses


Coding/ Billing Information

Note: 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:

<table>
<thead>
<tr>
<th>HCPES Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J1428</td>
<td>Injection, eteplirsen, 10 mg</td>
</tr>
</tbody>
</table>


References