Cigna Drug and Biologic Coverage Policy

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Next Review Date: 5/15/2019
Coverage Policy Number: 1702

Subject: Eteplirsen

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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

Cigna covers eteplirsen (Exondys 51™) as medically necessary when 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 ambulatory and capable of walking at least 200 meters in a 6 minute walk test (6MWT)

Initial authorization for 6 months. Reauthorization requires a documented diagnosis of Duchenne muscular dystrophy (DMD), confirmed mutation of the DMD gene that is amenable to exon 51 skipping and documentation of a positive clinical response, including remaining ambulatory.

Cigna does not cover the use of eteplirsen (Exondys 51) for any other indication because it is considered experimental, investigational or unproven.

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 eteplirsen (Exondys 51) therapy.

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

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.

**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

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**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. (Kinali, 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)

**Guidelines**
Guidelines are available from the American Academy of Neurology (2016) and the DMD Care Considerations Working Group (2010), which was selected by the Centers for Disease Control and Prevention. 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)

**Clinical Efficacy**
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.

**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.

**Covered when medically necessary:**

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C9484</td>
<td>Injection, eteplirsen, 10 mg (Code deleted 12/31/2017)</td>
</tr>
<tr>
<td>J1428</td>
<td>Injection, eteplirsen, 10 mg</td>
</tr>
</tbody>
</table>

**References**

8. Sarepta Therapeutics, Inc. Exondys 51 (eteplirsen) injection, for intravenous use [product information]. Cambridge, MA: Sarepta Therapeutics, Inc.; February 2018

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