Introduction

Exondys 51® (eteplirsen) and Vyondys 53™ (golodirsen) are new drugs used for Duchenne Muscular Dystrophy (DMD), which is a rare genetic disorder characterized by progressive muscle degeneration and weakness. It is caused by an absence of a functional dystrophin, which is a protein that helps keep muscle cells intact. Dystrophin gene is thought to be defective when its structure contains one or more exon deletions due to a genetic mutation. This disease primarily affects boys. Symptom onset is usually in early childhood, between ages 3 and 5. Muscle weakness can begin as early as age 3, first affecting the muscles of the hips, pelvic area, thighs and shoulders, and later the skeletal (voluntary) muscles in the arms, legs, and trunk. By the early teens, the heart and respiratory muscles also get affected, often requiring the use of assistive devices. Tests used to diagnose DMD vary from a blood test (measuring creatine kinase) to the muscle biopsy (measuring dystrophin protein levels), to the genetic testing (looking for the defective dystrophin gene).

Standard of therapy is aimed at slowing the loss of muscle strength to maximize the quality of life, and involves physical therapy and medications, such as steroids: prednisone and deflazacort. Assistive devices for breathing difficulties may also be used later in the stages of disease progression. Exon skipping treatments are a novel approach used in the management of this disease.
Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

We will review specific intravenous (IV) and injectable drugs for medical necessity for all ages.

For those age 13 and older, we also will review the site of service for medical necessity. Site of service is defined as the location where the drug is administered, such as a hospital-based outpatient setting, an infusion center, a physician's office, or at home. Click here to be directed to the site of service review criteria.

The following drug addressed in this policy is subject to site of service review:

- Exondys 51® (eteplirsen)

Note: Quantity limits for individual drugs can be found in Dosage and Quantity Limits.

<table>
<thead>
<tr>
<th>Site of Service Administration</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medically necessary sites of service</td>
<td>IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site:</td>
</tr>
<tr>
<td>- Physician's office</td>
<td>- These are the preferred medically necessary sites of service for specified drugs.</td>
</tr>
<tr>
<td>- Infusion center</td>
<td></td>
</tr>
<tr>
<td>- Home infusion</td>
<td></td>
</tr>
<tr>
<td>Hospital-based outpatient setting</td>
<td>IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site.</td>
</tr>
<tr>
<td>- Outpatient hospital IV infusion department</td>
<td></td>
</tr>
<tr>
<td>Site of Service Administration</td>
<td>Medical Necessity</td>
</tr>
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<td>--------------------------------</td>
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</tbody>
</table>
| Hospital-based outpatient clinical level of care | **This site is considered medically necessary for the first 90 days for the following:**  
- The initial course of infusion of a pharmacologic or biologic agent  
**OR**  
- Re-initiation of an agent after 6 months or longer following discontinuation of therapy*  

*Note: This does not include when standard dosing between infusions is 6 months or longer |

This site is considered medically necessary when there is no outpatient infusion center within 50 miles of the patient’s home and there is no contracted home infusion agency that will travel to their home, or a hospital is the only place that offers infusions of this drug.  

This site is considered medically necessary only when the patient has a clinical condition which puts him or her at increased risk of complications for infusions, including any ONE of the following:  
- Known cardiac condition (e.g., symptomatic cardiac arrhythmia) or pulmonary condition (e.g., significant respiratory disease, serious obstructive airway disease, %FVC ≤ 40%) that may increase the risk of an adverse reaction  
- Unstable renal function which decreases the ability to respond to fluids  
- Difficult or unstable vascular access  
- Acute mental status changes or cognitive conditions that impact the safety of infusion therapy  
- A known history of severe adverse drug reactions and/or anaphylaxis to prior treatment with a related or similar drug  

| Hospital-based outpatient setting | These sites are considered not medically necessary for infusion and injectable therapy services of various medical and biologic |
### Site of Service Administration

- Outpatient hospital IV infusion department
- Hospital-based outpatient clinical level of care

### Medical Necessity

agents when the site-of-service criteria in this policy are not met.

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### Drug

#### Antisense Oligonucleotides, IV

<table>
<thead>
<tr>
<th><strong>Exondys 51® (eteplirsen)</strong> IV</th>
<th><strong>Medical Necessity</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Exondys 51® (eteplirsen) is subject to review for site of service administration.</td>
<td></td>
</tr>
</tbody>
</table>

**Exondys 51® (eteplirsen) may be considered medically necessary for male patients up to 19 years of age when:**

- Patient has the diagnosis of Duchenne Muscular Dystrophy
  **AND**
- Patient has a confirmed mutation of the DMD gene that is amenable to exon 51 skipping:
  - Genetic testing is required to determine the specific DMD gene mutation for a definitive diagnosis
  **AND**
- Patient is able to ambulate (with or without assistance*) and complete a 6-minute-walk distance test of at least 250 meters
  - Record of the baseline 6MWT is necessary for the initial review
  **AND**
- Patient has been established on a stable dose of corticosteroids for at least 6 months
  **AND**
- Dose is limited to 30mg/kg IV once weekly

**Note:** Assistance not to include use of a wheelchair

<table>
<thead>
<tr>
<th><strong>Vyondys 53™ (golodirsen)</strong> IV</th>
<th><strong>Medical Necessity</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vyondys 53™ (golodirsen) may be considered medically necessary for male patients up to 15 years of age when:</td>
<td></td>
</tr>
</tbody>
</table>

- Patient has the diagnosis of Duchenne Muscular Dystrophy
  **AND**
**Drug** | **Medical Necessity**
--- | ---
**Antisense Oligonucleotides, IV**  |  - Patient has a confirmed mutation of the DMD gene that is amenable to **exon 53** skipping:
  - Genetic testing is required to determine the specific DMD gene mutation for a definitive diagnosis

  **AND**

  - Patient is able to ambulate (with or without assistance*) and complete a 6-minute-walk distance test of at least 250 meters
    - Record of the baseline 6MWT is necessary for the initial review

  **AND**

  - Patient has been established on a stable dose of corticosteroids for at least 6 months

  **AND**

  - Dose is limited to 30mg/kg IV once weekly

  *Note: Assistance not to include use of a wheelchair

**Corticosteroids, Oral**

| **Emflaza® (deflazacort) oral** | **Emflaza® (deflazacort) may be considered medically necessary for the following labeled indication:**
| --- | ---
|  |  - Treatment of Duchenne Muscular Dystrophy (DMD) in patients 2 years of age and older who have had an adequate trial* and treatment failure due to the lack of response or increase in adverse events with prednisone

  *Adequate trial is defined as 3 continuous months of therapy.

**Drug** | **Investigational**
--- | ---
**As listed** | **All other uses of the medications listed in this policy are considered investigational.**
<table>
<thead>
<tr>
<th>Approval</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial authorization</td>
<td>Exondys 51® (eteplirsen) and Vyondys 53™ (golodirsen) can be approved for 1 year. Emflaza® (deflazacort) can be approved for 6 months.</td>
</tr>
</tbody>
</table>
| Re-authorization criteria | Future re-authorization of Exondys 51® (eteplirsen) and Vyondys 53™ (golodirsen) depends on the clinical benefit/response shown at the time of reauthorization, where:  
- Patient does not show deterioration on 2 successive 6MWT measurements with 6 months interval over a year as compared to the baseline 6MWT measurement  
OR  
- Patient shows deterioration at a rate less than that expected, based on the natural history of the disease  
Future re-authorization of Emflaza® (deflazacort) requires documentation of continued clinical response, measured by improvement or stable muscle strength as compared to the baseline and/or diminished loss of muscle strength. |

**Documentation Requirements**

The patient’s medical records submitted for review should document that medical necessity criteria are met. The record should include the following:

- Office visit notes that contain the diagnosis, relevant history, genetic testing, physical evaluation and medication history
- Results of 6MWT tests for Exondys 51 and Vyondys 53

**Coding**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>HCPCS</td>
<td></td>
</tr>
<tr>
<td>J1428</td>
<td>Injection, eteplirsen (Exondys 51®), 10 mg</td>
</tr>
</tbody>
</table>
### Code Description

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J3590</td>
<td>Unclassified biologics (use only to report Vyondys 53™)</td>
</tr>
</tbody>
</table>

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

### Related Information

#### Benefit Application

Emflaza® (deflazacort) is managed through the pharmacy benefit. Exondys 51® (eteplirsen) and Vyondys 53™ (golodirsen) are managed through the medical benefit.

#### Definition of Terms

**6-Minute walk distance test (6MWD):** Test that measures the distance (in meters) a person is able to walk in 6 minutes. This measure helps to estimate disease burden by looking at the rate of ambulation.

**Antisense oligonucleotide (AON):** Antisense Oligonucleotides are synthetic polymers used to alter the synthesis of a particular protein. This is achieved by the binding of the antisense oligonucleotide to the messenger RNA from which that protein is normally made.

**Dystrophin gene:** Dystrophin gene provides a structural link between the muscle cytoskeleton and extracellular matrix to maintain muscle integrity. Dystrophin is the largest human gene, consisting of 2.4 million base pairs of DNA (with 79 exons). It is located primarily in muscles used for movement, such as skeletal muscles, and in the heart (cardiac) muscle. Small amounts of dystrophin are also present in nerve cells in the brain. In skeletal and cardiac muscles, dystrophin is a part of a group of proteins that work together to strengthen muscle fibers and protect them from injury as muscles contract and relax. Dystrophin acts as an anchor, connecting muscle cells with other molecules outside of the cell.

**Exon 51 skipping:** Molecular “patch” (in the form of a drug molecule) that allows exon skipping (in this case exon #51, as that is the affected exon, which accounts for 13% of DMD patients) to create a truncated form of a protein that is partially functional.
**Exon 53 skipping:** Molecular “patch” (in the form of a drug molecule) that allows exon skipping (in this case exon #53, as that is the affected exon, which accounts for 8% of DMD patients) to create a truncated form of a protein that is partially functional.

**Exons:** Exons are the sections of the DNA that code for the protein.

### Consideration of Age

The age described in this policy for Site of Service reviews for medical necessity is 13 years of age or older. The age criterion is based on the following: Pediatric patients are not small adults. Pediatric patients differ physiologically, developmentally, cognitively, and emotionally from adult patients, and vary by age groups from infancy to teen. Children often require smaller doses than adults, lower infusion rates, appropriately sized equipment, the right venipuncture site determined by therapy and age, and behavioral management during administration of care. Specialty infusion training is therefore necessary for pediatric IV insertions and therapy. Due to pediatric unique physiology and psychology, site of service review is limited to patients above the age of 13.

The use of this Exondys 51® (eteplirsen) for male patients up to 19 years of age is based on the clinical trial experience as described in the full prescribing information of the FDA label.

### Evidence Review

#### Description

Exondys 51® (eteplirsen) is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) subclass. PMOs are synthetic molecules in which the five-membered ribofuranosyl rings found in natural DNA and RNA are replaced by a six-membered morpholino ring. Each morpholino ring is linked through an uncharged phosphorodiamidate moiety rather than the negatively charged phosphate linkage that is present in natural DNA and RNA. Each phosphorodiamidate morpholino subunit contains one of the heterocyclic bases found in DNA (adenine, cytosine, guanine, or thymine). Eteplirsen contains 30 linked subunits.

Eteplirsen is 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. Exon skipping is intended to allow for production of an internally truncated dystrophin protein, which was evaluated in Study 2 and Study 3 (see below for details).

**Clinical Efficacy Data and Safety**

**Clinical Benefit**

The clinical benefit of Exondys 51® (eteplirsen) has not been established in clinical trials.

**Clinical Trials Experience (Adverse Reactions)**

In the Exondys 51® (eteplirsen) clinical development program, 107 patients received at least one intravenous dose of Exondys 51, ranging between 0.5 mg/kg (0.017 times the recommended dosage) and 50 mg/kg (1.7 times the recommended dosage). All patients were male and had genetically confirmed Duchenne muscular dystrophy. Age at study entry was 4 to 19 years. Most (89%) patients were Caucasian.

Eteplirsen was studied in a double-blind, placebo-controlled study for 24 weeks (Study 1), followed by an open label extension (Study 2). In Study 1, 12 patients were randomized to receive weekly intravenous infusions of Exondys 51 (n=8) or placebo (n=4) for 24 weeks. All 12 patients continued in Study 2 and received open-label Exondys 51 weekly for up to 208 weeks.

In Study 1, 4 patients received placebo, 4 patients received Exondys 51 30 mg/kg, and 4 patients received Exondys 51 50 mg/kg (1.7 times the recommended dosage). In Study 2, 6 patients received Exondys 51 30 mg/kg/week and 6 patients received Exondys 51 50 mg/kg/week.

Adverse reactions that occurred in 2 or more patients who received Exondys 51 and were more frequent than in the placebo group in Study 1 are presented in Table 1 (the 30 and 50 mg/kg groups are pooled). Because of the small numbers of patients, these represent crude frequencies that may not reflect the frequencies observed in practice. The 50 mg/kg once weekly dosing regimen of Exondys 51 is not recommended.
Table 1. Adverse Reactions in DMD Patients Treated with 30 or 50mg/kg/week Exondys 51 with Incidence at Least 25% More than Placebo (Study 1)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Exondys 51 (N=8) %</th>
<th>Placebo (N=4) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balance disorder</td>
<td>38</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>38</td>
<td>0</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>25</td>
<td>0</td>
</tr>
</tbody>
</table>

The most common adverse reactions were balance disorder and vomiting. In the 88 patients who received ≥30 mg/kg/week of Exondys 51 for up to 208 weeks in clinical studies, the following events were reported in ≥10% of patients and occurred more frequently than on the same dose in Study 1: vomiting, contusion, excoriation, arthralgia, rash, catheter site pain, and upper respiratory tract infection. There have been reports of transient erythema, facial flushing, and elevated temperature occurring on days of Exondys 51 infusion.

Clinical Studies

Registration Trials

Exondys 51® (eteplirsen) was evaluated in three clinical studies in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

In Study 1, patients were randomized to receive weekly infusions of Exondys 51 (30 mg/kg, n=4); Exondys 51 (50 mg/kg, n=4), or placebo (n=4) for 24 weeks. The primary endpoint was dystrophin production; a clinical outcome measure, the 6-minute walk test (6MWT), was also assessed. The 6MWT measures the distance that a patient can walk on a flat, hard surface in a period of 6 minutes. Patients had a mean age of 9.4 years, a mean 6-minute walk distance (6MWD) at baseline of 363 meters, and were on a stable dose of corticosteroids for at least 6 months. There was no significant difference in change in 6MWD between patients treated with Exondys 51 and those treated with placebo. All 12 patients who participated in Study 1 continued treatment with open-label Exondys 51 weekly for an additional 4 years in Study 2. The 4 patients who had been randomized to placebo were re-randomized 1:1 to Exondys 30 or 50 mg/kg/week such that there were 6 patients on each dose. Patients who participated in Study 2 were compared to an external control group. The primary clinical efficacy outcome measure was the 6MWT. Eleven patients in Study 2 had a muscle biopsy after 180 weeks of treatment with
Exondys 51, which was analyzed for dystrophin protein level by Western blot. Study 2 failed to provide evidence of a clinical benefit of Exondys 51 compared to the external control group. The average dystrophin protein level after 180 weeks of treatment with EXONDYS 51 was 0.93% of the dystrophin level in healthy subjects. Because of insufficient information on dystrophin protein levels before treatment with Exondys 51 in Study 1, it is not possible to estimate dystrophin production in response to Exondys 51 in Study 1.

Additional pulmonary endpoints were monitored in the 4 year open-label safety extension study and included measures of FVC (forced vital capacity), MIP (maximum inspiratory pressure), and MEP (maximum expiratory pressure). Loss of pulmonary function is a key contributor to mortality in patients with DMD and this study provides clinically relevant endpoints regarding the efficacy of Exondys 51. Individuals in the Exondys 51 treated group (n=12) experienced a decline in predicted FVC by 2.3% while the natural history cohort experienced a decline of 4.1%, suggesting Exondys 51 may have a role in slowing disease progression and preserving pulmonary function.

Table 2. Western Blot Results: Exondys 51-Treated (Week 48) vs. Pretreatment Baseline (% Normal Dystrophin)

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Baseline % normal dystrophin</th>
<th>Week 48 % normal dystrophin</th>
<th>Change from Baseline % normal dystrophin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.13</td>
<td>0.26</td>
<td>0.13</td>
</tr>
<tr>
<td>2</td>
<td>0.35</td>
<td>0.36</td>
<td>0.01</td>
</tr>
<tr>
<td>3</td>
<td>0.06</td>
<td>0.37</td>
<td>0.31</td>
</tr>
<tr>
<td>4</td>
<td>0.04</td>
<td>0.10</td>
<td>0.06</td>
</tr>
<tr>
<td>5</td>
<td>0.17</td>
<td>1.02</td>
<td>0.85</td>
</tr>
<tr>
<td>6</td>
<td>0.37</td>
<td>0.30</td>
<td>-0.07</td>
</tr>
<tr>
<td>7</td>
<td>0.17</td>
<td>0.42</td>
<td>0.25</td>
</tr>
<tr>
<td>8</td>
<td>0.24</td>
<td>1.57</td>
<td>1.33</td>
</tr>
<tr>
<td>9</td>
<td>0.11</td>
<td>0.12</td>
<td>0.01</td>
</tr>
<tr>
<td>10</td>
<td>0.05</td>
<td>0.47</td>
<td>0.43</td>
</tr>
<tr>
<td>11</td>
<td>0.02</td>
<td>0.09</td>
<td>0.07</td>
</tr>
<tr>
<td>12</td>
<td>0.18</td>
<td>0.21</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean</td>
<td>0.16</td>
<td>0.44</td>
<td>0.28; p=0.008</td>
</tr>
</tbody>
</table>
In Study 3, 13 patients were treated with open-label Exondys 51 (30 mg/kg) weekly for 48 weeks and had a muscle biopsy at baseline and after 48 weeks of treatment. Patients had a mean age of 8.9 years and were on a stable dose of corticosteroids for at least 6 months. Dystrophin levels in muscle tissue were assessed by Western blot. In the 12 patients with evaluable results, the pre-treatment dystrophin level was 0.16% ± 0.12% (mean ± standard deviation) of the dystrophin level in a healthy subject and 0.44% ± 0.43% after 48 weeks of treatment with EXONDYS 51 ($p < 0.05$). The median increase after 48 weeks was 0.1%.

There were a number of issues with the design and execution of these studies, as discussed by Irwin and Herink (2017).

**Additional Data Analyses**

A systematic review by Randeree and Eslick, published March 2018, found four studies. A pooled analysis was inconclusive as to whether increase in percentage dystrophin-positive fibers and distance walked is clinically significant. The authors concluded that further evidence is required.

Kinane, et al. Published a five year follow up analysis of patients in the original trial cohort of 12 patients using respiratory endpoints: forced vital capacity (FVC), maximum expiratory pressure (MEP) and maximum inspiratory pressure (MIP). FVC was compared to historical controls from the United Dystrophinopathy Project (UDP, N=34), MEP and MIP were compared to published natural history rates of decline. The authors reported that their age-adjusted mixed-model repeated-measures analysis showed decreases of 2.3% and 2.6% annually for FVC% predicted and MEP% predicted, and an annual increase of 0.6% for MIP% predicted for the eteplirsen-treated cohort. Data from the UDP demonstrated a 4.1% decline in FVC% predicted.

The UDP cohort was chosen as a comparator for FVC because their data were carefully collected and patients were similar in demographics and treatment protocols to those in the eteplirsen trials. These data do support the conclusion that there is a decreased decline in respiratory function as measured by FVC, to approximately half that of the comparators. Although not a primary endpoint in the original trials, FVC is an appropriate marker of clinical function because end stage DMD involves the usual complications of respiratory compromise.
**Vyondys 53 (golodirsen)**

Golodirsen has been studied in a single, unpublished, Phase 1/2 trial, Study 101. Part 1 consisted of a 12-week, double-blind, placebo-controlled, Phase 1 study which randomized 12 boys with genetically confirmed DMD amenable to exon 53 skipping to golodirsen or placebo. The patients were 6-15 years of age with mean 6MWT of ≥250 meters, and stable pulmonary and cardiac function. Those randomized to golodirsen received 4 mg/kg IV weekly for 2 weeks, followed by 10, 20, and 30 mg/kg each for 2 weeks. The primary outcome measures were AEs and serious adverse events (SAEs). All patients reported at least one treatment-emergent adverse event (TEAE); however, these were not described. No severe TEAE or discontinuations due to AEs occurred. Moderate TEAE occurred in two patients (pyrexia and a Staphylococcus aureus Port-A-Cath infection). No further safety results were provided. Secondary outcome measures found the time to maximum concentration (Tmax) of golodirsen was 1.01-1.22 hours and the half-life ranged from 3.2-3.4 hours.

Part 2 of Study 101 consisted of a 144-week, open-label, Phase 2 trial conducted in 25 patients treated with golodirsen. All patients from the Phase 1 trial continued to the Phase 2 trial. Additionally, 24 patients with DMD who were not amenable to exon 53 skipping were included as an untreated group. The co-primary outcomes were change from BL in total distance walked in the 6MWT at week 144 and change from BL in dystrophin protein level at week 48. The 6MWT results are not yet available. Golodirsen significantly increased the mean (± SD) change in percent normal dystrophin at week 48 compared to BL (1.02% ± 1.03% (range 0.09%-4.3%) vs 0.095% ± 0.068% (range 0.02%-0.31%) golodirsen vs BL, mean change 0.92% ± 1.01, p<0.001). This was a 16-fold increase in dystrophin compared to BL. Median change from BL was 0.88%. No data from the untreated group was reported. Secondary outcome measures in Part 2 of Study 101 found exon 53 skipping increased from 2.6% at BL to 19% at week 48. A positive correlation was noted between exon skipping and dystrophin expression (r=0.5, p=0.011). Restoration of the reading frame was confirmed in all patients who were assessed via Sanger deoxyribonucleic acid (DNA) sequence analysis of polymerase chain reaction (PCR)-amplified products (n not reported). The mean ± SD percentage of dystrophin-positive fibers (PDPF) at week 48 was 10.47% ± 10.10% with golodirsen compared to 1.43% ± 2.04 at BL (p<0.001).

Golodirsen is also being studied in the on-going ESSENCE trial, a double-blind, placebo-controlled, Phase 3 trial which randomizes patients 7-13 years of age with DMD amenable to either exon 45 or 53 skipping to active drug (golodirsen or casimersen) or placebo for 96 weeks.
**Practice Guidelines and Position Statements**


In children with DMD, prednisone should be offered for improving strength (Level B) and pulmonary function (Level B). Prednisone may be offered for improving timed motor function (Level C), reducing the need for scoliosis surgery (Level C), and delaying cardiomyopathy onset by 18 years of age (Level C). Deflazacort may be offered for improving strength and timed motor function and delaying age at loss of ambulation by 1.4–2.5 years (Level C). Deflazacort may be offered for improving pulmonary function, reducing the need for scoliosis surgery, delaying cardiomyopathy onset, and increasing survival at 5–15 years of follow-up (Level C for each). Deflazacort and prednisone may be equivalent in improving motor function (Level C). Prednisone may be associated with greater weight gain in the first years of treatment than deflazacort (Level C). Deflazacort may be associated with a greater risk of cataracts than prednisone (Level C). The preferred dosing regimen of prednisone is 0.75 mg/kg/d (Level B). Over 12 months, prednisone 10 mg/kg/weekend is equally effective (Level B), with no long-term data available. Prednisone 0.75 mg/kg/d is associated with significant risk of weight gain, hirsutism, and cushingoid appearance (Level B).

**Medicare National Coverage**

There is no national coverage determination.

**CADTH Review**

CADTH, the Canadian national health technology assessment agency, published a review of novel therapies for DMD in June 2017. The review outlines the various approaches to treatment currently available or under investigation:

Corticosteroids and assistive devices remain the mainstay of therapy. Prednisone is recommended first line. Deflazacort, available in Europe and recently approved in the U.S., may cause less weight gain, but at several orders of magnitude higher cost.
Eteplirsen (Exondys 51)

Eteplirsen is a third-generation synthetic antisense oligonucleotide (AON) that is designed to induce exon 51 skipping. The most frequent mutations in the dystrophin gene occur between exons 45 and 55, and exon 51 accounts for 13% of DMD. Exon 51 skipping results in partial production of a truncated dystrophin protein and, consequently, partially preserves dystrophin function. Exon skipping works in cases of deletions, but not duplications because AONs cannot differentiate between the original and duplicated exons. It was granted accelerated approval by FDA, based on minimal trial results (see above), with further confirmation required. Exon 51 skipping enables the defective gene to produce functioning dystrophin.

Ataluren (Translarna)

Ataluren suppresses nonsense mutations, which enables the production of a modified dystrophin protein. Approximately 10% to 15% of males with DMD who have a point mutation involving a premature stop codon, producing a shortened and dysfunctional dystrophin protein. Ataluren enables read-through of the premature stop codon and production of a modified dystrophin protein. The resulting increase in dystrophin production would be expected to stabilize or slow disease progression. Ataluren selects only premature stop codons, not normal ones. Small placebo-controlled studies failed to produce statistically significant and meaningful results, possibly due to lack of power, resulting in an unfavorable risk/benefit estimate. It was approved by EMA but not by FDA. It is also approved in several other countries ex-US.

Ezutromid

Ezutromid is an utrophin modulator that aims to replace lost dystrophin with utrophin, which has protein-binding properties similar to dystrophin and shares 80% of its sequence. It is produced during the early stages of muscle-fiber development and switched off in maturing muscle as dystrophin is produced. Muscle damage upregulates utrophin production to promote repair. Utrophin modulators have the advantage of being potentially applicable to all DMD patients, irrespective of the underlying genetic defect. Ezutromid is in phase IIa and has not yet achieved regulatory approval anywhere.
**Givinostat**

Givinostat is a histone deacetylase inhibitor that may help to rebalance the repair process in muscle by increasing muscle regeneration. Histone deacetylase inhibitor activity is upregulated in dystrophic muscles and impairs muscle regeneration. Like Ezutromid, it would be expected to benefit all DMD patients but is unapproved. A phase I single-arm trial failed to show that givinostat improves functional outcomes.

**Idebenone**

Idebenone (also unapproved) is an ATP production modulator that helps dystrophic muscle cells maintain their cellular energy supply and protects cells from oxidative stress. Like ataluren, it has safety concerns.

**CADTH Conclusions**

Current access to DMD drugs is limited, as patients in Canada are generally restricted to participation in clinical trials. Many studies are recruiting by invitation only. [This reflects the high demand and desperation of patients and their families. It suggests that extremely small and underpowered trials could have been made larger.] Once approved, a major barrier is likely to be cost. Some of the medications may be used in combination, further increasing the economic burden. Criteria will need to be determined to establish which patients are more likely to benefit, and to identify when a drug is no longer beneficial.

Administering medication to children can be challenging. Idebenone and ataluren require multiple oral daily doses. This route may not be ideal in DMD patients who have trouble swallowing, although ataluren is available as granules for suspension. Eteplirsen is infused IV weekly, which could be a barrier.

**2018 Update**

A detailed literature search for new clinical data from 1/1/17 to 5/11/18 and scan of 2016 for registration trial data missing from publication were performed (none was found). Additional data analyses and report from CADTH (2017) added. References updated.
2019 Update

A detailed literature search for new clinical data from 5/1/18 to 2/28/19 found no further evidence requiring change to this policy.

References


16. Reviewed and approved by the P&T Committee 5/30/18.


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>01/01/17</td>
<td>New policy, approved December 13, 2016. Add to Prescription Drug Section.</td>
</tr>
<tr>
<td>04/01/17</td>
<td>Annual Review, approved March 14, 2017. Updated criteria based on the P&amp;T Committee’s expert recommendation provided at a quarterly P&amp;T meeting.</td>
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<tr>
<td>01/01/18</td>
<td>Coding update, added HCPCS code J1428 (new code effective 1/1/18).</td>
</tr>
<tr>
<td>02/01/18</td>
<td>Interim Review, approved January 16, 2018; effective June 1, 2018, Exondys 51® (eteplirsen) becomes subject to review for site of service administration.</td>
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<tr>
<td>02/14/18</td>
<td>Annual Review, approved February 6, 2018. Policy updated with literature review through December 2017. Information added regarding the effect on pulmonary function from 4 year, open-label study. No change to the policy statement. Approved February 13, 2018, to update hospital based outpatient coverage from 30 days to 90 days.</td>
</tr>
<tr>
<td>06/01/18</td>
<td>Minor update; removed note and link to updated policy. Site of Service criteria becomes effective.</td>
</tr>
<tr>
<td>09/21/18</td>
<td>Minor update. Added Consideration of Age statements.</td>
</tr>
<tr>
<td>11/01/18</td>
<td>Minor update, the Site of Service criteria was updated for clarity.</td>
</tr>
<tr>
<td>01/01/19</td>
<td>Minor update. Clarified Consideration of Age information.</td>
</tr>
<tr>
<td>04/01/19</td>
<td>Annual Review, approved March 19, 2019. Updated literature search. No changes.</td>
</tr>
</tbody>
</table>

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and
local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2020 Premera All Rights Reserved.

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  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
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Email AppealsDepartmentInquiries@Premera.com

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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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