Exondys 51® (eteplirsen) is a new drug 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 (not available in US). Assistive devices for breathing difficulties may also be used later in the stages of disease progression. Exon skipping (such as Exondys 51 injection) is a novel approach used in the management of this disease.
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>
</table>
| Medically necessary sites of service  | IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site:  
  - These are the preferred medically necessary sites of service for specified drugs.  |
| Hospital-based outpatient setting  | IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site.  
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  |
### Site of Service Administration

<table>
<thead>
<tr>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>discontinuation of therapy*</td>
</tr>
</tbody>
</table>

*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

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

These sites are considered not medically necessary for infusion and injectable therapy services of various medical and biologic agents when the site-of-service criteria in this policy are not met.

### Drug

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

### Medical Necessity

**administration.**

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 ~363 (+/-) 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 once weekly

*Note: Assistance not to include use of a wheelchair

## Drug

### Investigational

Exondys 51® (eteplirsen) is considered investigational for all other uses not outlined in this policy, as well as for patients with Duchenne Muscular Dystrophy who do not have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

## Approval

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Exondys 51® (eteplirsen) can be approved for 1 year.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial authorization</td>
<td>Future re-authorization depends on the clinical benefit/response shown at the time of reauthorization, where:</td>
</tr>
<tr>
<td>Re-authorization criteria</td>
<td>Patient does not show deterioration on 2 successive 6MWT</td>
</tr>
</tbody>
</table>
Approval | Criteria
--- | ---
 | 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

Dosage and Quantity Limits

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosage and Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duchenne Muscular Dystrophy</td>
<td>30 mg/kg once weekly</td>
</tr>
</tbody>
</table>

Documentation Requirements

Initial authorization

*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 relevant history and physical and testing

**AND**

- Results of 6MWT tests as stated above

Reauthorization

- Records showing a total of three 6MWT measurements, one at baseline and two 6 months apart in a given year are necessary for re-authorization review

Coding

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

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 50 mg/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.
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.

**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).
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.

### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<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>
</tr>
<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>
</tr>
<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>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------------------------------------------------------</td>
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<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>

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Deutsche (German):

Italiano (Italian):