Drug Use Research & Management Program
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New Drug Evaluation: Eteplirsen injection, intravenous

Date of Review: July 2017
Generic Name: eteplirsen injection

End Date of Literature Search: 06/02/2017
Brand Name (Manufacturer): Exondys 51 (Sarepta Therapeutics, Inc.)
Dossier Received: Yes

Research Questions:

1. What is the efficacy of eteplirsen compared to placebo or currently available treatments of Duchenne Muscular Dystrophy (DMD)?
2. Is eteplirsen safe for treatment of DMD?
3. Are there any subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) that would particularly benefit or be harmed from treatment with eteplirsen?

Conclusions:

- Efficacy of eteplirsen for DMD remains to be established. Studies failed to demonstrate improvement in functional outcomes even in patients treated for more than 4 years, and labeling for eteplirsen specifies that a clinical benefit has not been established.[1] Furthermore, though a slight change in level of dystrophin level was observed (<1% of normal), changes do not correlate with any clinical improvement. Additionally, there are significant methodological concerns and a high risk of bias in available studies.
- There is insufficient evidence that eteplirsen treatment in patients with DMD is associated with any clinical change in symptoms or functional status. Functional improvement was primarily evaluated using the 6-minute walk test (6MWT). In a single study of 12 patients, no difference was observed between patients treated with eteplirsen and placebo in the 6MWT at 24 or 48 weeks.[1] A long-term extension study evaluating functional improvement assessed with the 6MWT or North Star Ambulatory Assessment (NSAA) over 36 months compared eteplirsen to a historical control group.[2] However, significant limitations associated with this study including differing baseline characteristics between groups, inability to control for potential confounders, and differences in assessment methods limit confidence in these results. Labeling for eteplirsen specifies that a clinical benefit has not been established.[3]
- Eteplirsen was primarily evaluated in 2 studies (n=24) which examined change in the level of dystrophin protein. After 3.5 years of treatment, patients treated with eteplirsen had an average dystrophin level that was 0.93% of the normal protein level in healthy patients (as evaluated by Western blot).[1] Mean change in dystrophin level from baseline to 48 weeks was 0.28% of normal (0.16% at baseline vs. 0.44% at 48 weeks; p=0.008).[1] Change in dystrophin protein level has not been validated as a surrogate outcome in DMD and there is no evidence to support it is correlated to clinical outcomes. The minimum change in dystrophin level which may result in a clinical improvement has not been established.
- There is insufficient evidence to evaluate safety of eteplirsen for treatment of DMD. The safety population included a total of 114 patients treated with at least one dose of eteplirsen. Only 36 patients have been treated for more than 6 months and 12 have been treated for more than 1 year.[1] Serious adverse events occurred in 6 patients (5.3%) and were consistent with expected events for a population of patients with DMD.[1]
- There is insufficient evidence to evaluate differences in specific populations or subgroups.

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Date: July 2017

Recommendations:

- Recommend implementation of prior authorization criteria limiting use to the population studied and requiring maintained functional status with continuation of therapy (**Appendix 2**).
- Due to the lack of evidence supporting clinical efficacy of eteplirsen for the treatment of Duchenne muscular dystrophy, consider referral of eteplirsen to the Health Evidence Review Commission (HERC) for funding placement as a medication with high cost and no clinically meaningful benefit.

Background:

Duchenne muscular dystrophy (DMD) is a rare X-linked genetic disorder which results in the absence of a functional dystrophin protein. Duchenne's is the most common type of muscular dystrophy occurring in approximately 1 in 5000 to 7250 patients age 5 to 24 years.[1,4] Currently, in the Oregon Health Plan (OHP) population, approximately 70 fee-for-service patients and more than 300 patients enrolled in coordinated care organizations have a diagnosis of muscular dystrophy. Available claims data for OHP is unable to distinguish between patients with various types of muscular dystrophy. Based on this data and the estimated prevalence of mutations amenable to exon 51 skipping, approximately 3-4 OHP patients may be eligible for this medication. Without a functional dystrophin protein, muscle fibers degenerate and are eventually replaced with adipose and fibrotic tissue.[1] Patients with DMD experience progressive muscle deterioration leading to pulmonary problems, dilated cardiomyopathy, arrhythmias, and increased risk for thrombotic events. In many patients, these complications lead to wheelchair dependence between the ages of 8-16 and death before the age of 20.[1,5] Only 25% of patients remain ambulatory by age 16.[1] There is currently no curative treatment, and therapy focuses on improving symptoms, enhancing quality of life, and decreasing disease progression.[4] Guidelines from the American Academy of Neurology recommend glucocorticoids as first-line treatment in children over 5 years of age to improve muscle and pulmonary function and reduce risk of scoliosis.[5] Other non-pharmacological therapies which are often essential in disease management include physical therapy and use of support devices such as braces and wheelchairs.[4] As the disease progresses, mechanical ventilation and spinal surgery may be used to improve pulmonary function and decrease pain from scoliosis and vertebral fractures.[4]

Recently the FDA approved eteplirsen, an oligonucleotide indicated for patients with DMD who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.[3] In approximately 13% of patients with DMD, exon 51 is included in pre-mRNA and one or more nearby exons are deleted.[1] This results in a shift in the reading-frame as the protein is formed and leads to reduction or absence of dystrophin protein. Eteplirsen binds to exon 51 of dystrophin pre-mRNA leading to exclusion of this exon, partially restoring the reading-frame, and forming a potentially functional, truncated dystrophin protein. In untreated patients with DMD, documented dystrophin levels typically range from 0 to 0.4% of normal healthy patients.[1] Experts suggests that dystrophin levels less than 3% of normal are typically associated with a phenotype of DMD.[1] It is unclear whether increases in dystrophin protein level in patients with DMD correlate to clinical outcomes. Similarly, the minimum change in dystrophin level which may result in a clinical improvement has not been established. Some experts suggest that very minimal improvements may constitute a beneficial change in dystrophin level while others suggest that dystrophin levels at 10-20% of normal would likely correlate to clinically significant changes in muscle symptoms or function.[1,6] In patients with Becker muscular dystrophy, a less severe form of the muscular dystrophy, dystrophin protein levels are on average 80% of normal.[1]

Efficacy outcomes which are clinically important in patients with DMD include muscle strength, functional status, quality of life, disease progression, and mortality. Functional improvement is often evaluated using the 6-minute walk test (6MWT) and the North Star Ambulatory Assessment (NSAA) score. The 6MWT evaluates the distance a patient is able to walk in 6 minutes and evaluates both function and endurance.[7] In healthy children less than 7 years of age, the distance patients are able to walk is expected to remain stable or improve over time with estimated mean walk distances ranging from 500-700 meters.[2,8,9] The minimum clinically important difference in the 6MWT for patients with DMD is approximately 30 meters.[7] The NSAA evaluates 17 functional activities including standing, walking, standing up from a chair, standing on 1 leg, climbing/descending step, moving from lying to sitting, rising from the floor, jumping, hopping,

and running.[1] Each item is evaluated on a 3 point scale with a total score ranging from 0 to 34. NSAA scores less than 16 are more often correlated with 6MWT of less than 300 meters and scores greater than 30 correlate moderately with 6MWT of more than 400 meters.[10] The NSAA is considered a more comprehensive measure of functional status compared to other functional assessments, but score is often very dependent on patient effort.[1] The minimum clinically important difference in NSAA score has not been determined. Other functional assessments include timed measures of rising from a sitting or supine position, 10-meter run/walking time, or time to climb 4 stairs.[7]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Eteplirsen was evaluated in 3 poor quality studies with significant flaws (1 randomized placebo controlled trial and 2 open-label studies). All patients in these trials were ambulatory and on a stable dose of corticosteroids for at least 6 months. Study 1 was a double-blind, randomized, dose-response, placebo-controlled study for 24 weeks. It included 12 white, male, pediatric patients (age range 7-13, mean 9.4 years) with a mean 6-minute walking distance at baseline of 363 meters (substantially decreased from the mean distance of 500-700 meters expected in healthy children).[11] Patients were randomized (1:1:1) to eteplirsen 50 mg/kg weekly, eteplirsen 30 mg/kg weekly, or placebo.[11] After 24 weeks, patients were enrolled in a long-term open-label extension study (Study 2). In this study, patients initially randomized to the placebo group were re-randomized to eteplirsen 30 or 50 mg/kg/week for which data is available up to 240 weeks (4.6 years).[1] The primary outcomes for these studies included the level of dystrophin protein in muscle tissue (measured as a percentage of the expected normal levels in healthy patients without DMD) and change in the 6MWT.[11] Study 3 is an ongoing, unpublished, interim analysis of an open-label study which evaluated the change in dystrophin levels for 13 male patients treated with eteplirsen 30 mg/kg weekly for up to 48 weeks.[1]

No difference was observed in the 6MWT at 24 weeks compared to placebo.[11] In addition, the long-term extension study failed to demonstrate a statistically significant difference in 6MWT upon comparison to placebo at 48 weeks.[1] Since all patients were re-randomized to treatment, the manufacturer attempted to compare eteplirsen to a control group generated from two DMD natural history cohorts of patients in an open-label extension of the primary study. Patients were matched to 13 historical controls based on corticosteroid use, available longitudinal data for the 6MWT, age (less than or greater than 7 years), and genotype.[1,2] Patients were not matched on the basis of the 6MWT distance though mean distance was similar between groups at baseline (363 vs. 358 meters).[2] Overall, compared to the historical control, patients treated with eteplirsen experienced a benefit of 162 meters at 36 months (3 years) in the 6MWT ($p=0.0005$).[1] The manufacturer also claimed that only 2 patients (16.7%) treated with eteplirsen lost ambulation over 4 years compared to 76.9% (10/13) of untreated historical controls.[1] However, when results are evaluated as a function of age, 6 patients (4 less than 14 years of age and 2 still ambulatory between 13 and 14 years of age) appear to have similar disease progression and functional decline compared to their age-matched, untreated historical controls.[1] All patients treated with eteplirsen had progressive decline in other functional outcomes including NSAA scores with no apparent difference from the untreated historical control.[1]

There are significant concerns and inherent limitations of using a historical control group and conclusions cannot be made from this fatally flawed study. Performance on the 6MWT is susceptible to expectation bias and coaching which significantly confounds the benefit observed in an open-label trial when compared to a historical cohort. For example, in patients treated with eteplirsen, the maximum distance achieved in the 6MWT was recorded, whereas the standard approach for historical controls was to classify patients as non-ambulatory if they were unable to complete the 6MWT.[1] If a standard assessment for the 6MWT was applied to both groups, several patients treated with eteplirsen may have been classified as non-ambulatory. It is also unclear whether physical therapy programs were similar between the treatment group and historical control.[1,2] In addition, there were significant differences between groups in steroid

regimens used and the mean age at initiation of steroid treatment (6.4 years in historical control vs. 5.2 years in treatment group).[1] These differences affect interpretation and bias results in favor of eteplirsen treatment. Historical control patients also had a lower mean NSAA scores at baseline, indicating greater disease severity and could bias results in favor of eteplirsen treatment.[1] The historical control population was selected after publication of results in eteplirsen trials and was not specified *a priori.* There is a high risk of selection, performance, detection, and reporting bias in this study and efficacy results should not be considered in the decision-making process.

The additional outcome in Study 1 and 2 was mean change in percent of dystrophin-positive fibers from baseline.[1] Biopsies through week 48 were collected from the biceps and week 180 biopsies were collected from the deltoid.[1] Because different muscle groups are known to have varying levels of dystrophin protein, comparisons of the deltoid biopsy at week 180 to earlier samples taken from the biceps are difficult to interpret. Evaluation of a different muscle group may result in varying levels of dystrophin protein. Dystrophin level was assessed using both immunofluorescence and Western blot techniques. These provide very different insight into perceived benefit of eteplirsen. Western blot is a quantitative method whereas immunofluorescence is used to identify localization of a protein in a particular tissue and is considered to be less quantitative.[1] Due to significant methodological and technical issues with the initial analyses, the FDA concluded that the results were unreliable and uninterpretable.[12] The FDA required a blinded re-analysis of available biopsies by 3 independent evaluators.[1]

After 3.5 years of treatment, patients treated with eteplirsen (both 30 and 50 mg/kg/week) had an average dystrophin level that was 0.93% of the normal protein level in healthy patients (as evaluated by Western blot).[1] Approximately one-third of patients had no change in dystrophin level or changes that were below the level of quantification (0.24% of normal).[1] Only one patient had a dystrophin level greater than 2% and none had a level greater than 3% of normal.[1] Overall, re-analyzed biopsies did not confirm the initial study findings and did not support the dose dependent effect seen in earlier trials. In addition, there was a poor correlation between results of immunofluorescence and Western blot analyses, and results of the immunofluorescent tests varied between treatment groups.

Despite re-analysis of biopsy samples, there are several significant limitations which should be taken into consideration. Only 3 patients had baseline samples that were evaluable upon re-analysis, and therefore, the change in dystrophin level from baseline could not be assessed.[1] Furthermore, immunofluorescent samples at 48 weeks (11 months) and Western blot analysis at 180 weeks (3.5 years) were processed differently and were not comparable with earlier samples.[1] There was also significant intra-patient variability upon Western blot analysis at 180 weeks. At least 3 patients had analyses which differed by more than 0.7% of normal between samples evaluated at 180 weeks.[1] Furthermore, the methods used to select the group of historical controls is unclear, and they may not represent a random sample of comparative patients, decreasing confidence in the results which indicate protein level was only 0.93% of normal.[1] In addition, biopsy samples were stored for approximately 3 years before re-analyzed and the stability of the protein over time was not evaluated.[1]

Study 3 is an ongoing, unpublished, open-label study including 13 male patients treated with eteplirsen 30 mg/kg weekly for up to 48 weeks (mean age of 8.9 years).[1] Data was available from 12 of these patients.[1] The primary outcome evaluated change in dystrophin protein level (evaluated using Western blot analysis). No functional outcomes were evaluated in this study. Protein levels that were below the level of quantification (0.24%) were analyzed using several imputation methods including minimum (0%), maximum (0.24%), and actual measured values. Results were consistent between all analyses, and demonstrated statistically significant differences in dystrophin level compared to baseline.[1] Mean change in dystrophin level from baseline to 48 weeks was 0.28% of normal (0.16% at baseline vs. 0.44% at 48 weeks; p=0.008).[1] At 48 weeks, approximately 60% of patients treated in this study had no change in dystrophin level or had a change less than 0.25% compared to the normal level in a health patient. Only one patient had a dystrophin level greater than 1% and none had a level greater than 2% of normal.[1] These changes in dystrophin levels are not clinically significant and do not translate into any clinical meaningful benefit.

Efficacy of eteplirsen for DMD remains to be established. Data from Western blot analysis suggests that some patients may not respond to treatment with little to no improvement in dystrophin levels.[1] The FDA recommended further post-marketing studies to evaluate efficacy at higher doses.[1] Studies failed to demonstrate improvement in functional outcomes even in patients treated for more than 4 years, and labeling for eteplirsen specifies that a clinical benefit has not been established.[1] Furthermore, though a slight change in level of dystrophin level was observed (<1% of normal), changes did not correlate with any clinical improvement. It remains to be determined if changes in dystrophin correlate to clinical outcomes, and the FDA has required further studies to evaluate functional improvements in patients with DMD.[3] FDA approval of eteplirsen was highly controversial because it conflicted with the recommendation by the external advisory committee who expressed multiple concerns with the studies, including: industry funding, blinding procedures, assays used, small sample size, and very minimal change from baseline.

Clinical Safety:

The safety population included a total of 114 patients treated with at least 1 dose of eteplirsen. Only 36 patients have been treated for more than 6 months and 12 have been treated for more than 1 year.[1] Because the population is small and the majority of these trials were not placebo-controlled, there is limited data available regarding adverse effects and safety. Serious adverse events occurred in 6 patients (5.3%) and included wound infection, vomiting, fractures, decreased oxygen saturation, and viral lymphadenitis.[1] All events were thought to be unrelated to treatment. One patient, who had preexisting cardiomyopathy, experienced a decreased left ventricular ejection and discontinued treatment.[1] In general, serious and severe adverse effects were consistent with expected events for a population of patients with DMD. However, there is insufficient data to assess short-term or long-term safety of eteplirsen.

Table 1. Pharmacology and Pharmacokinetic Properties.[3]

Parameter	
Mechanism of Action	Eteplirsen binds 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. Skipping of exon 51 allows for formation of a truncated dystrophin protein.
Distribution and Protein Binding	Protein binding: 6-17% Volume of distribution at steady state: 600 mL/kg
Elimination	Approximately 67% of eteplirsen is renally cleared Majority of drug elimination occurred within 24 hours
Half-Life	3-4 hours
Metabolism	No hepatic metabolism apparent

Abbreviations:

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Functional or symptom improvement
2) Quality of life
3) Disease progression
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Mean change in the percentage of dystrophin-positive fibers
2) Change in the 6-minute walk test at 48 weeks

Table 2. Comparative Evidence Table.

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Mendell, et al. 2013.[11] Exondys 51 FDA Medical Review.[1] Exondys 51 FDA Summary Review.[12] DB, PC, Phase IIB RCT	1. Eteplirsen 30 mg/kg/ week 2. Eteplirsen 50 mg/kg/ week 3. Placebo/ delayed tx After 24 weeks patients in the placebo group were randomized to one of the treatment groups in an open label extension study up to 48 weeks. Patients have been continued in the extension study for greater than 4 years.	Demographics: - Mean age: 9.4 years - Deflazacort 18-25 mg/day: 8/12 (67%) - Prednisone: 4/12 (33%) - Mean 6MWT: 363 m (range 261-456) Key Inclusion Criteria: - Boys age 7 to 13 - Confirmed DMD deletions potentially correctable by exon 51 skipping - 6MWT of 200-400 m - On stable glucocorticoid tx for ≥24 weeks - Stable cardiac and pulmonary function Key Exclusion Criteria: - None	ITT: 1. 4 2. 4 3. 4 mITT: 1. 2 2. 4 3. 4 Attrition: All patients completed 48 weeks	Primary Endpoints (ITT):[1] Mean change in percent of dystrophin-positive fibers from baseline to 12 or 24 weeks[T]** 1. 13% 2. 2% 3. -1% P-values NR Mean change in percent of dystrophin-positive fibers from baseline to 48 weeks** 1. 9% 2. 10% 3. -1% P-values NR Mean percent of normal dystrophin at 180 weeks (SD) with Western blot analysis[12] 1. 0.96% (0.95) 2. 0.91% (0.79) Mean change in 6MWT at 48 weeks (SE) 1. -153.4 m (38.7) 2. 21 m (38.2) 3. -68.4 m (37.6) p-values NR Secondary Endpoints (ITT): Mean change in 6MWT at 24 weeks (SE) 1. -128.2 m (31.6) 2. -0.3 m (31.2) 3. -25.8 m (30.6) p-values NR	NA NA NA NA	No serious or treatment -emergent adverse effects reported at 48 weeks.	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: UNCLEAR. Randomization methods and allocation concealment were unclear. Average baseline 6MWT in patients randomized to 30 mg/kg/week was ~40 m less than other groups. Performance Bias: UNCLEAR. Methods of blinding were not stated. Placebo consisted of phosphate buffered saline. Placebo or eteplirsen was diluted in normal saline and infused over 60 minutes. Detection Bias: HIGH. Biopsy samples were not processed consistently at all time points leading to unclear changes over time. Use of immunofluorescent staining was less quantitative than Western blot analysis. Re-analysis by blinded, independent pathologists (reported here) resulted in significantly differing protein levels. Analysis confirmed by Western blot at 180 weeks. Multiple methodological limitations reduce confidence in the results and limit ability to make conclusions regarding dystrophin level. Attrition Bias: HIGH. All patients remained in the study up to 48 weeks. Use of ITT appropriate. The mITT population excludes 2 patients who had rapid disease progression and became non-ambulatory despite treatment and increases in dystrophin-positive fibers. Reporting Bias: HIGH. Funding provided by Sarepta Therapeutics who was involved in data interpretation and editing the manuscript. Results of multiple post-hoc analyses emphasized. Results of immunofluorescent assays may be misleading as they describe the percent of fibers stained with an intensity ***above the background of the image*** and DO NOT correspond to a percent of normal levels expected in a healthy patient. **Applicability**: Patient: Small population limits ability to make conclusions. Patients were on stable dose of corticosteroid and ambulatory at baseline. Intervention: Effective dose not established. Comparator: Placebo appropriate to determine efficacy. No dose-response observed. Use of an open-label, non-controlled extension study after 24 weeks limits ability to make long-term efficacy or safety conclusions. Outcomes: Dystrophin measured using immunofluorescence, confirmed by Western blot. As reported, outcomes do not correspond to percent of normal levels expected in a healthy patient and may be misleading. Due to significant methodological issues, the change from baseline could not be determined. Correlation of 6MWT or other functional outcomes with dystrophin levels is unclear. Setting: Initial 24 weeks conducted at Nationwide Children's Hospital, open-label extension study conducted at 10 sites throughout the United States.

Abbreviations [alphabetical order]: 6MWT = 6 minute walk test; ARR = absolute risk reduction; CI = confidence interval; DB = double blind; ITT = intention to treat; m = meters; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; PC = placebo-controlled; PP = per protocol, RCT = randomized controlled trial; SE = standard error; tx = treatment

Percentages were evaluated with immunofluorescent assays and represent the percent of fibers stained with an intensity ***above the background* of the image and DO NOT correspond to a percent of normal levels expected in a healthy patient.

[†]Data for 30mg/kg/week group collected at 24 weeks, 50mg/kg/week collected at 12 weeks, and placebo collected at both times.

References:

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use EXONDYS 51™ safely and effectively. See full prescribing information for EXONDYS 51.

EXONDYS 51 (eteplirsen) injection, for intravenous use
Initial U.S. Approval: 2016

INDICATIONS AND USAGE

EXONDYS 51 is an antisense oligonucleotide 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. (1)

DOSAGE AND ADMINISTRATION

- 30 milligrams per kilogram of body weight once weekly (2.1)
- Administer as an intravenous infusion over 35 to 60 minutes (2.1, 2.3)
- Dilution required prior to administration (2.2)

DOSAGE FORMS AND STRENGTHS

Injection:

- 100 mg/2 mL (50 mg/mL) in single-dose vial (3)
- 500 mg/10 mL (50 mg/mL) in single-dose vial (3)

CONTRAINDICATIONS

None (4)

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥35% and higher than placebo) were balance disorder and vomiting (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sarepta Therapeutics, Inc. at 1-888-SAREPTA (1-888-727-3782) or FDA at 1-800FDA-1088 or *www.fda.gov/medwatch*.
Revised: 09/2016

Appendix 2: Prior Authorization Criteria

Drugs for Duchenne Muscular Dystrophy

Goal(s):
- Encourage use of corticosteroids which have demonstrated long-term efficacy
- Restrict use of eteplirsen and deflazacort to patients with Duchenne Muscular Dystrophy and limit use of deflazacort to patients with contraindications or serious intolerance to other oral corticosteroids

Length of Authorization:
- 6 months

Requires PA:
- Eteplirsen
- Deflazacort

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is the request for treatment of Duchenne Muscular Dystrophy?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness. Note: Eteplirsen and deflazacort are not indicated for other forms of muscular dystrophy or other diagnoses.
4. Is the request for continuation of eteplirsen treatment?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5

Approval Criteria		
5. Is the request for deflazacort?	**Yes:** Go to #6	**No:** Go to #8
6. Is the patient ≥ 5 years of age?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Does the patient have a documented contraindication or intolerance to oral prednisone that is not expected to crossover to deflazacort?	**Yes:** Approve for up to 12 months. Document contraindication or intolerance reaction.	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of another oral corticosteroid.
8. Does the patient have a diagnosis of Duchenne Muscular Dystrophy with one of the following genetic mutations amenable to exon 51 skipping: • Deletion of exons 45 to 50 • Deletion of exons 48 to 50 • Deletion of exons 49 and 50 • Deletion of exon 50 OR • Deletion of exon 52?	**Yes:** Go to #9 Document genetic testing.	**No:** Pass to RPh, Deny; medical appropriateness.
9. Has the patient been on a stable dose of corticosteroid for at least 6 months?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.
10. Has baseline functional assessment been evaluated using a validated tool such as the 6-minute walk test or North Star Ambulatory Assessment?	**Yes:** Document baseline functional assessment and approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Has the patient's baseline functional status been maintained at or above baseline level or not declined more than expected given the natural disease progression?	**Yes:** Approve for up to 6 months Document functional status.	**No:** Pass to RPh, Deny; medical appropriateness.

P&T/DUR Review: *07/17 (SS)*
Implementation: *TBD*