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OHSU Drug Effectiveness Review Project Summary Report – **Deflazacort** oral tablet

Date of Review: July 2017
Generic Name: deflazacort

End Date of Literature Searcy: 05/22/2017
Brand Name (Manufacturer): Emflaza™ (PTC Therapeutics)
Dossier Received: Yes

Research Questions:

1. What is the comparative efficacy or effectiveness of deflazacort compared to currently available corticosteroids in improving clinical outcomes (including improved muscle strength and mobility, prevention of long-term cardiac and pulmonary complications, and increased survival) in patients with Duchenne Muscular Dystrophy (DMD)?
2. Is deflazacort safe for treatment of DMD and what is the relative safety compared to other corticosteroids?
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 deflazacort?

Conclusions:

- The report conducted by the Drug Effectiveness Review Project (DERP) evaluated deflazacort for the treatment of DMD based on 4 randomized controlled trials (RCT), 3 systematic reviews, and one guideline.
- Four RCTs of poor methodological quality showed insufficient evidence that demonstrated no difference in muscle strength and motor outcomes between deflazacort and prednisone for patients with DMD.
- Similarly, there is a lack of quality evidence evaluating comparative differences in adverse effects between deflazacort and prednisone. Evidence that deflazacort is associated with significantly less weight gain (mean difference [MD] 2.91 to 4.1 kg) but more cataracts than prednisone was of insufficient quality. Due to significant methodological limitations of these trials and lack of reported data, the true treatment effect is likely to be substantially different from the estimated treatment effect. Two of these RCTs were completed more than 20 years ago, and only one included patients in the United States. As a result, these data may not be applicable to patients under the Oregon Health Plan (OHP) today. There was no comparative evidence of deflazacort and prednisone beyond 2 years of follow-up.
- There is insufficient evidence to evaluate differences between deflazacort and other corticosteroids for DMD or other conditions.
- Overall, there is insufficient evidence to evaluate differences in adverse effects between deflazacort and other oral corticosteroids. Evidence is limited by small sample sizes, lack of reported methodology and outcomes, and inadequate data in a United States population of patients.

Recommendations:

- Implement prior authorization criteria that restricts use to patients with DMD and documented contraindication or serious intolerance to oral corticosteroids (**Appendix 3**).

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- Refer deflazacort to the Health Evidence Review Commission (HERC) for funding placement as a drug with high cost and marginal benefit compared to currently available low-cost oral corticosteroids.

Background:
Duchenne muscular dystrophy (DMD) is a rare X-linked genetic disorder caused by the absence of a functional dystrophin protein. Duchenne's is the most common type of muscular dystrophy occurring in approximately 1 in 7250 males between the ages of 5 to 24 years.[1] 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 are unable to distinguish between patients with various types of muscular dystrophy. Based on the estimated prevalence of DMD, approximately 60 OHP patients with muscular dystrophy may be eligible for this medication. Patients with DMD experience progressive muscle deterioration leading to loss of ambulation and decreased muscle strength. Long-term complications include pulmonary problems, dilated cardiomyopathy, arrhythmias, and increased risk for thrombotic events. In many patients, these complications can lead to wheelchair dependence by age 12 and death before the age of 20.[2] Only 25% of patients remain ambulatory by age 16.[3] There is currently no curative treatment, and therapy focuses on improving symptoms, enhancing quality of life, and decreasing disease progression. Guidelines from the American Academy of Neurology recommend either deflazacort or prednisone as first-line treatment in children over 5 years of age to improve muscle and pulmonary function and reduce risk of scoliosis.[2] Other non-pharmacological therapies which are often essential in disease management include physical therapy and use of support devices such as braces and wheelchairs. 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]

Deflazacort is a corticosteroid which has been on the market in Europe and other countries for decades, but only recently achieved FDA approval in the United States. Deflazacort was approved through the FDA priority review process for the treatment of DMD in patients age 5 years and older based on the results of 2 randomized active-comparator trials including 196 and 18 patients each. The primary outcome evaluated change in muscle strength measured by a modified Medical Research Council scale. The Medical Research Council scale (MRC) ranges from 0 to 10 points, with higher scores indicating greater strength. A score of 10 indicates the muscle is able to contract against full resistance and 0 represents no movement observed.[1] Scores are typically assessed and summarized for several muscle groups in several positions (sitting, prone, supine, and lying on the side). The minimum clinically important difference with this scale has not been established. Other studies evaluated change in muscle function using timed function tests such as the time required to stand from a supine position or the time required to walk a certain distance. Other methods to evaluate functional improvement included use of the Motor Function Index which evaluates a patient's ability to climb four 17 cm stairs, stand from a sitting position, and walk 10 meters on flat ground.[5] Each test is evaluated on a 1-3 scale indicating if individuals are able to complete the task without assistance (1 point), accomplish the task with assistance (2 points), or are not able to complete the task (3 points).[5] Total scores range from 3 to 9 with larger scores indicating more severe disease.[5] The validity of this scale and minimum clinically important change has not been determined.

Deflazacort has also been studied for treatment on multiple conditions including idiopathic thrombocytic purpura, essential mixed cryoglobulinemia, juvenile chronic arthritis, nephrotic syndrome, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus, solid organ transplant rejection, and urolithiasis.[4] Randomized controlled trials have examined the efficacy or safety of deflazacort compared to other corticosteroids. However, long-term population-based studies indicate that oral prednisone may be associated with greater incidence of weight gain, hirsutism and cushingoid appearance, while deflazacort may have greater risk of cataracts.[1,6,7] The DERP review summarizes comparative evidence of deflazacort versus other corticosteroids for the treatment of DMD. Evidence for other potential off-label conditions will also be considered in this report.

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Methods:
An April 2017 Drug Effectiveness Review Project (DERP) report compared deflazacort to prednisone for children with Duchenne Muscular Dystrophy was used to inform recommendations for this drug evaluation. The DERP report was supplemented with information from the manufacturer's prescribing information and the FDA website. In addition, new evidence published since completion of the DERP report that evaluated use for FDA-approved indications or off-label conditions was identified. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The DERP is part of the Pacific Northwest Evidence-based Practice Center at Oregon Health & Science University. The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. DERP reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports. The original DERP report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publically available in the agenda packet and on the DURM website.

Summary Findings: Duchenne Muscular Dystrophy
A total of 4 RCTs, 3 systematic reviews, and one guideline were identified in the DERP report. All trials included a similar population of patients (males at least age 5 with DMD), and all compared FDA-approved dosing of deflazacort 0.9 mg/kg/day to prednisone 0.75 mg/kg/day.[2] Overall evidence from these trials was graded as poor quality due to significant methodological flaws and lack of reported data.[2]

The primary study used for FDA approval included 196 males from the United States and Canada randomized to deflazacort 0.9 mg/kg/day, deflazacort 1.2 mg/kg/day, prednisone 0.75 mg/kg/day, or placebo.[2] At 12 weeks, patients in the placebo group were re-randomized to a treatment arm. The trial was completed in 1995, and at this time the distinction between types of muscular dystrophy was not well defined. As a result, this trial included patients with either Duchenne or Becker muscular dystrophy limiting applicability to patients with DMD today. The primary outcome was change in muscle strength at 12 weeks measured using a modified MRC index score.[1] Scores are based on several muscle strength assessments and evaluated on a 0 to 10 point rating scale with lower scores indicating more severe disease.[1,8] Secondary outcomes included muscle strength at 1 year, motor function, pulmonary function, disease severity, adverse effects, weight gain and change in growth. Outcomes are summarized in **Table 1**. Actual MRC scores at baseline, 12 weeks and 1 year were not reported and numbers represent the change in MRC score from baseline. Overall, there was no significant difference in muscle strength between patients treated with either corticosteroid at 12 weeks or 1 year.[2] Compared to placebo at 12 weeks, these differences in MRC were statistically significant for both groups, though the clinical significance of 0.25 to 0.38 points is questionable.[8] There was no difference between deflazacort and prednisone in timed motor function tests between groups at 1 year.[2] Timed motor function tests included time to stand from a supine position, climb 4 stairs, run or walk 30 feet, or propel a wheelchair 30 feet.[2] This evidence had several important limitations which decrease confidence in these results including potential conflicts of interest and lack of information on randomization methods, allocation concealment, and baseline disease severity between groups.

Table 1. Mean change in MRC Score^ from Baseline (95% CI).[8]

	12 weeks	1 year
Placebo	-0.1 (-0.23 to 0.03)	-
Deflazacort 0.9 mg/kg	0.15 (0.01 to 0.28)*	0.39 (0.25 to 0.54)
Deflazacort 1.2 mg/kg	0.26 (0.12 to 0.40)*	0.38 (0.23 to 0.54)
Prednisone 0.75 mg/kg	0.27 (0.13 to 0.41)*	0.23 (0.07 to 0.38)

*Statistically different from placebo.
^MRC score was evaluated on a 0 to 10 point scale.

A second trial of 100 German patients also evaluated the comparative efficacy and safety of prednisone and deflazacort.[2] Overall, data from this study were rated as poor quality due to significant methodological flaws and lack of reported data. Preliminary results of this RCT including 67 patients were published in 1995 and final results including all 100 patients were available in an unpublished conference report in 2000.[2] Of the 100 patients enrolled, 80% remained in the trial at 2 years.[2] Overall, there was no difference in muscle function or strength between groups. However, numerical data for these outcomes were not reported, and results from this trial were limited by highly disparate attrition rates between groups without use of an intention-to-treat analysis.[2]

The third RCT was double-blinded and included 18 Italian patients followed for 2 years.[2] Patients were randomized to prednisone or deflazacort and reportedly stratified by disease severity and age.[2] However, methods used for randomization and allocation concealment were unclear.[2] Outcomes reported at 1 and 2 years included muscle strength, motor outcomes (reported descriptively) and weight gain. No difference was observed in muscle strength or functional scores at 2 years.[2] This study was significantly limited by the small sample size, lack of reported outcomes, and significant risk of bias.[2]

Another RCT evaluated 34 Iranian patients randomized to deflazacort or prednisone.[2] The study was limited by poor reporting of methodological methods including methods of randomization, allocation concealment, blinding, and baseline characteristics for each group.[2] In addition, a significant portion of patients were lost to follow up with high differential rates between groups (17.6% in deflazacort vs. 29.4% in prednisone group) increasing risk of bias.[2] The efficacy outcomes evaluated included change in the motor function index (**Table 2**) up to 18 months. The motor function index evaluates functional status on a 7-point scale (range 3-9) with larger scores indicating more severe disease.[5] At 12 months, patients treated with deflazacort had a statistically significant increase from baseline in the mean motor function index compared to prednisone, but differences failed to achieve statistical significance at 18 months.[2,5]

Table 2. Motor function index reported as mean score (95% CI) and mean difference (MD) from baseline.[5]

	Baseline	12 months	18 months
Deflazacort 0.9 mg/kg	4.93 (95% CI 4.4 to 5.5)	4.36 (95% CI 3.7 to 5.0); MD -0.57	4.64 (95% CI 3.8 to 5.5); MD -0.29
Prednisone 0.75 mg/kg	5.0 (95% CI 4.6 to 5.5)	5.25 (95% CI 4.4 to 6.1); MD 0.25	5.75 (95% CI 4.4 to 7.2); MD 0.75
Mean difference between groups		0.82; p=0.001	1.04; p=0.128

Three systematic reviews also evaluated comparative efficacy and safety between prednisone and deflazacort.[2] Though the RCTs included in these reviews differed, they all reached similar conclusions. Evidence for motor outcomes was graded as insufficient to very low quality demonstrating no difference in efficacy between deflazacort and prednisone.[2]

One guideline from the American Academy of Neurology on use of corticosteroids for treatment of DMD was included in the DERP report. Evidence supporting recommendations in this guideline included one RCT and multiple observational studies that evaluated the comparative effectiveness of deflazacort and prednisone.[2] The majority of observational evidence included cohort or case-control studies with a defined control group, masked outcome assessment, and description of potential confounding factors.[9] Overall, evidence was graded as moderate quality indicating moderate assessment of benefit versus risk, low quality indicating small benefit relative to risk, or very low quality indicating there is insufficient evidence to evaluate risk versus benefit. Due to limitations in the evidence, many recommendations are graded as low quality.[2] No specific recommendations are made for any particular agent. Evidence supporting use of prednisone to improve strength and pulmonary function was rated as moderate quality.[2] There was low quality evidence to support use of deflazacort to improve strength and pulmonary function, delay loss of ambulation by 1.4 to 2.5 years, and increase survival at 5 or 15 years.[2] Evidence regarding survival was primarily derived from 3 observational studies which demonstrated increased mortality in untreated patients (21-43%) compared to those treated with deflazacort (3-11%).[6] Six observational studies evaluated outcomes of muscle strength and ambulation with deflazacort treatment and demonstrated improvements in motor outcomes using various measures.[6] In 3 of these studies, the age at which patients lost ambulation was improved by 1.4 to 2.5 years in patients treated with deflazacort compared to no treatment.[6] Two additional studies evaluating both prednisone and deflazacort demonstrated improvements in age at loss of ambulation for both medications.[6] Evidence evaluating the need for scoliosis surgery, delaying the onset of cardiomyopathy, and improving timed motor function tests was evaluated as low quality for both prednisone and deflazacort.[2] Similarly, there was low quality evidence that deflazacort and prednisone provide similar improvements in motor function, and low quality evidence that deflazacort has less weight gain but greater risk for cataracts than prednisone.[2] Direct comparative evidence included 2 observational studies that demonstrated no difference in functional motor outcomes over 1 year and 5.49 years each.[6] In these studies, weight gain was more common in the first year of treatment (mean weight increase of 21.3% with prednisone vs. 9% with deflazacort) corresponding to a mean weight increase at 1 year of 5.08 kg in patients treated with prednisone compared to 2.17 kg in patients treated with deflazacort ($p<0.05$).[6] However, one study noted no difference in weight in older children (12-15 years).[6] Cataracts occurred more often in patients treated with deflazacort compared to prednisone, though results were not statistically significant.[6] There was insufficient evidence to compare differences between therapies for other outcomes including pulmonary and cardiac function.[2]

Evidence evaluating adverse effects was also reported from these 4 RCTs. In the primary study used for FDA approval (n=196), patients randomized to deflazacort had less weight gain (5.05 kg) compared to prednisone (8.45 kg; MD 3.4 kg; $p<0.0001$) over the course of 1 year. However, incidence of cataracts was higher with deflazacort (6.6%) at 1 year compared to prednisone (4.4%; p-value not reported).[2] Similar trends were noted between groups with evaluation of body mass index.[2] Similarly in subsequent studies, patients treated with prednisone versus deflazacort reported higher incidence of weight gain leading to treatment discontinuation (data not reported) and more weight gain at 1 and 2 years (2.17 kg vs. 5.08 kg, p-value not reported and 4.6 kg vs. 8.7 kg; $p<0.05$, respectively). Another study reported that patients treated with prednisone had a greater mean percent increase in weight than patients treated with deflazacort at 12 months (21.7% vs. 13.0%; $p=0.001$) and 18 months (32% vs. 21.7%; $p=0.046$) corresponding to a mean 2.41 to 3.18 kg weight increase in patients treated with prednisone compared to deflazacort.[2,5] One other study (n=100) also reported that more patients on deflazacort developed cataracts compared to patients treated with prednisone (36% vs. 3%, p-value not reported).[2] However, evidence from these RCTs was limited by inadequate or unclear methods, lack of adequately reported data, and high and/or disparate attrition rates without use of intention-to-treat analyses.[2] Systematic reviews evaluating adverse effects of deflazacort and prednisone also concluded that deflazacort was associated with less weight gain than prednisone though evidence was graded as very low quality indicating very little confidence in the estimated effect.[2] Further studies are needed to evaluate comparative safety and adverse effects between deflazacort and other corticosteroids.

Because deflazacort is a corticosteroid, FDA labelling includes warnings and precautions for adverse effects which have been associated with corticosteroid use. Warnings are summarized in **Appendix 1**. Additional rare but serious adverse effects include effects on growth and development, myopathy, Kaposi's sarcoma, thrombotic events, and anaphylaxis.[10] Deflazacort suspension also includes benzyl alcohol preservative which has been associated with increased risk of serious and fatal reactions in infants and is not approved in children less than 5 years of age.[10] Common adverse effects (occurring in >10% of patients compared to placebo at 12 weeks) included cushingoid appearance, weight gain, and increased appetite.[10] Because clinical trials included a limited population of patients randomized to deflazacort and placebo (n=51 and 50), rates of adverse events may not be reflective of rates observed in clinical practice.[10]

Off-label Indications

A high-quality systematic review published in 2012 examined the comparative efficacy and safety of deflazacort versus other corticosteroids for the treatment of nephrotic syndrome.[11] The review included 3 single-center RCTs (n=91 patients total) in France, Denmark and Argentina.[11] Patients were randomized to deflazacort or prednisone in 2 studies and to deflazacort or methylprednisolone in the third study.[11] Two trials evaluated use in children and one evaluated adults with newly diagnosed nephrotic syndrome. Data for these trials were described descriptively as they did not consistently report similar outcomes and evaluated different populations. Two studies examine time to remission, with no apparent difference between patients randomized to deflazacort or another corticosteroid.[11] In 1 study, the mean number of new relapses and the proportion of children who were relapse free at 1 year was improved with treatment of deflazacort compared to prednisone (MD 1.9; 0.9 vs. 2.8; $p<0.002$ and 60% vs. 10%; $p=0.002$, respectively).[11] Another study reported no difference in the number of relapses after more than 4 years of follow-up.[11] No significant difference was observed in mean growth velocity, fasting blood sugar, infection rate, or cushingoid symptoms when deflazacort was compared to other corticosteroids.[11] One study did report a smaller mean decrease with deflazacort compared to prednisone in bone density (3.6 vs. 5.9 gHa; $p<0.05$) and bone mineral content (0.0050 vs. 0.0089 gHa/cm^2/month; $p<0.05$) of the spine, while another study failed to achieve statistical significance between groups.[11] Evidence was limited by lack of defined primary and secondary outcomes and small patient population.[11] In addition, one trial failed to report adequate randomization methods, and in another, providers and outcome assessors were not blinded, increasing risk of bias.[11]

Randomized Controlled Trials:

A total of 155 citations were manually reviewed from the initial literature search. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. After further review, 139 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), population (eg, healthy subjects), or outcome (eg, non-clinical). Several excluded trials examined effects on bone mineral density or content. However, bone mineral density can vary between instruments and trials did not report outcomes using standardized methods (i.e. T-score or Z-score) making interpretation of these outcomes difficult. The remaining 20 trials were critically evaluated for internal validity and risk of bias. Seven trials were excluded due to substantial flaws and lack of reported methods which significantly increase risk for selection bias (i.e. methods of randomization and allocation concealment, inclusion and exclusion criteria, and relevant baseline characteristics were not reported), and results should not be considered in the decision-making process. Results of the remaining trials which evaluate evidence for deflazacort in off-label conditions are summarized in the table below. Overall, evidence is limited by small population size, significant methodological flaws, and lack of reported outcomes which increases risk of bias. In addition, the majority of studies were completed outside the United States at a single medical center, and published more than 15 years ago limiting applicability to the OHP population today.

Table 3. Description of Comparative Clinical Trials.

Study/Location	Comparison	Population/ Location	Primary Outcome	Results	Study Limitations and Potential Sources of Bias
Grosso S, et al. 2008.[12] OL, RCT N=35 Duration: 6 months	1. Hydrocortisone daily and tapered at monthly intervals on the following schedule: 10 mg/kg, 5 mg/kg, 2.5 mg/kg, 1 mg/kg, and 1 mg/kg on alternate days, thereafter 2. Deflazacort 0.75 mg/kg	Children with drug-resistant epilepsy Italy	Proportion of patients with >50% decreased seizure frequency at 6 months	1. 44% 2. 47% P=0.9	Patients and providers were not blinded and patients were allocated to groups on an alternate basis at hospitalization increasing risk of bias. Allocation concealment was not reported.
Elli A, et al. 1993.[13] Single-center, OL, RCT N=50 Duration: 1 yr	1. Deflazacort 2. Methylprednisolone Dosing administered in a ratio of 6 mg deflazacort to 4 mg methylprednisolone. Dose was tapered to 12 or 18 mg at 12 months.	Kidney transplant patients Italy	No primary outcome specified. Clinical outcomes included rejection episodes and weight gain at 1 year	Acute rejection episodes 1. 9 (36%) 2. 11 (44%) p-value NS Mean change in weight 1. 1.25 kg 2. 2.8 kg P<0.05	Inclusion and exclusion criteria were not specified. Randomization and allocation concealment methods were unclear. Baseline weight was higher in patients treated with methylprednisolone (2.7kg). Open-label study increases risk of bias. Primary and secondary outcomes were not specified and multiple outcomes were examined without methods to control for multiplicity increasing risk of reporting bias.
Kim Y, et al. 1997.[14] OL, single-site, RCT N=82	1. Deflazacort 2. Prednisolone Dose given in a ratio of 1 mg to 1.2 mg of prednisone to deflazacort	Kidney transplant patients with pre- or post-transplant DM Korea	No primary outcome specified. Outcomes included change in body weight, insulin requirements, acute rejection, adverse effects	50% dose reduction of insulin or diabetic agents 1. 12 (30.8%) 2. 2 (5%) P=0.023 Weight 1. 1.74 kg weight loss 2. 0.58 kg weight loss	Randomization and allocation concealment, methods were unclear. Primary and secondary outcomes were not specified and multiple outcomes were examined without methods to control for multiplicity increasing risk of bias.
Ferraris JR, et al. 2007.[15] OL, MC, RCT N=31 Duration: 3 yrs	1. Deflazacort 0.3 mg/kg/day 2. Methylprednisolone 0.2 mg/kg/day	Children following kidney transplantation (mean time since transplantation was 2.1 years) Argentina	No primary outcome specified. Outcomes included rates of adverse effects compared to baseline (growth, body weight, BMD, and effects on	No specified primary outcome. Multiple outcomes described descriptively. BMI was not significantly different between groups. More patients treated with deflazacort had an LDL<100 mg/dL (p<0.001) and normal	Randomization and allocation concealment methods were unclear. Patients and providers were not blinded increasing risk of bias. Primary and secondary outcomes were not pre-specified and were evaluated post-hoc. Adverse effects were evaluated using multiple analyses increasing risk of reporting bias. Multiple outcomes were described descriptively. Use of concomitant lipid or glucose-lowering therapies was not

			glucose and lipid metabolism).	glucose/insulin ratio (p=0.02) at 2 or 3 years.	addressed. Four patients (13%) were withdrawn from the study due to onset of puberty.
Saviola GL, et al. 2007.[16] Single-center, OL, cross-over, RCT N=21 Duration: 1 yr	1. Deflazacort 7.5 mg/day 2. Methylprednisolone 4 mg/day At 6 months, patients were allocated to the alternate treatment group	Adults with active RA or psoriatic arthritis, naïve to steroid treatment Italy	No specified primary outcomes. Efficacy was evaluated using ACR score at 6 and 12 months.	ACR50 at 6 months 1. 5/9 (55.5%) 2. 6/11 (54.5%) p-value NR ACR50 at 12 months 1. 6/9 (66.7%) 2. 7/11 (63.6%) p-value NR	Randomization and allocation concealment methods not stated. Patients and providers were not blinded increasing risk of bias. Primary and secondary outcomes were not specified.
Messina O, et al. 1992.[17] DB, RCT N=16 Duration: 1 yr	1. Deflazacort 12 mg/day 2. Prednisone 10 mg/day	Patients with RA Argentina	No primary outcome specified. Clinical outcomes included change in joint involvement, morning stiffness, and physical activity 12 months.	Changes in joint involvement, and morning stiffness NR. Change in physical activity was NS (described descriptively).	Blinding performed with identical capsules. Randomization generated with use of a computer with allocation concealment. Primary and secondary outcomes were not specified and multiple outcomes were examined without methods to control for multiplicity increasing risk of bias. Study not powered to determine differences in outcomes.
Loftus J, et al. 1991.[18] DB, RCT N=34 Duration: 1 yr	1. Deflazacort (mean dose 9.07 mg/day) 2. Prednisone (mean dose 7.87 mg/day) Corticosteroids administered as alternate-day regimens and in a 1.2 to 1 mg ratio of deflazacort to prednisone	Children with chronic juvenile rheumatoid arthritis England	No primary outcome specified. Outcomes included joint count, height, weight, and fractures.	No specified primary outcome. No statistical difference was noted in joint count, height, or fractures. Weight gain at 1 year was greater for prednisone than deflazacort; p<0.02 (described descriptively)	Randomization and blinding methods were not reported. Baseline weight was not reported. Primary and secondary outcomes were not specified and multiple outcomes were examined without methods to control for multiplicity increasing risk of bias. Study was not powered to determine differences in outcomes. Data on weight outcomes was not reported.
Gray R, et al. 1991.[19] Blinded, RCT N=26	1. Deflazacort 2. Prednisone Dose was fixed for first 15 days then adjusted based on clinical requirements	Adults with RA, polymyalgia rheumatic, mixed connective tissue disease, or severe eczema	No primary outcome specified. Clinical outcomes included weight, early morning stiffness, grip strength, pain and functional	No primary outcome specified. No statistically significant differences were observed between treatment groups for all clinical outcomes.	Randomization and allocation concealment methods were not reported. Patients blinded using identically packaged medications. Blinding of providers unclear. Primary and secondary outcomes were not specified and multiple outcomes were examined without methods to control for multiplicity increasing risk of bias. Study was

Duration: 3 months			assessments, and adverse effects		not powered to determine differences in outcomes. More patients in the deflazacort group began additional immunotherapy at the start of the study.
Di Munno O, et al. 1995.[20] Cross-over, DB, RCT N=31 Duration: 12 weeks	1. Deflazacort 24 mg daily 2. Deflazacort 48 mg on alternate days 3. Methylprednisolone 16 mg daily 4. Methylprednisolone 32 mg on alternate days After 2 weeks, dose was titrated based on clinical response. At 6 weeks patients were allocated to the alternate dosing regimen (daily vs. alternate day).	Polymyalgia rheumatica	No primary outcome specified. Clinical outcomes included pain scores (evaluated by visual analogue scale) and morning stiffness	Mean pain scores 1. -4.5 2. -4.6 3. -6.3 4. -6.0 p-values NS between all Mean change in morning stiffness from baseline (minutes) 1. -83 2. -84 3. -132 4. -116	Randomization and allocation concealment methods were unclear. Blinding achieved with use of identical packaging though tablets had different appearances. 7 patients (23%) were excluded from the analysis. Primary and secondary outcomes were not specified and multiple outcomes were examined without methods to control for multiplicity increasing risk of reporting bias.
Eberhardt R, et al. 1994.[21] DB, MC, RCT N=76 Duration: 12 months	1. Deflazacort 2. Prednisone Mean daily dose was 8.5 mg deflazacort and 7.3 mg prednisone.	Patients with RA Germany	Ritchie Index (an evaluation of 53 joint groups each scored on a 0-3 scale; total range: 0 to 159)	Ritchie index at 12 months (SD) 1. 12.8 (7.46) 2. 9.8 (7.6) P=0.4954	Randomization, allocation concealment, and blinding methods were unclear. Concomitant use of other medications for RA and baseline disease severity were not reported. 23 patients (30%) were lost to follow-up.
Lund B, et al. 1987.[22] DB, cross-over, RCT N=30	1. Deflazacort 2. Prednisone Dosing administered in a ratio of 1.2-1.8 mg deflazacort to 1 mg prednisone for 2 week periods	Patients with polymyalgia rheumatic Denmark	Disease activity, pain and tenderness evaluated using a visual analog scale	Results described descriptively. No difference was observed in general disease activity, pain or tenderness.	Randomization methods were unclear and baseline disease severity for each group was not reported. Multiple analyses performed without methods to control for multiplicity. Study not powered to determine differences in outcomes.
Rizzato G, et al. 1997.[23] OL, RCT	1. Deflazacort 2. Prednisone	Patients with chronic pulmonary sarcoidosis	No primary outcome specified. Clinical outcomes	Fractures 1. 1/28 (3.5%) 2. 5/30 (16.7%) p-value NR	Randomization and allocation concealment methods were unclear. Disease duration was longer for patients treated with deflazacort (5.6 vs. 3.5 years). Dose and duration of

N=72 Mean duration: 42 months	Mean starting dose was 22 mg for each group and tapered based on clinical requirements		included fracture events		treatment were not equivalent. Open-label trial further increases risk of bias. Primary and secondary outcomes were not specified and multiple outcomes were examined without methods to control for multiplicity increasing risk of bias. Bone toxicity analysis only reported in 58 patients (80%).
Ferrari A, et al. 1991.[24] OL, RCT N=27 Duration: 24 weeks	1. Deflazacort 1.4 mg/kg/day 2. Prednisone 1 mg/kg/day Treatment was tapered upon complete response to treatment (platelet count >150) or completion of 4 weeks of treatment	Autoimmune thrombocytopenic purpura	No primary outcome specified. Clinical efficacy outcomes included complete response (platelet count >150) and no response (platelet count <50) after 24 weeks	Complete response 1. 2/11 (18%) 2. 2/12 (17%) No treatment response 1. 4/11 (36%) 2. 4/12 (33%) p-values NS	Randomization and allocation concealment methods were unclear. Open label design increases risk of bias. Primary and secondary outcomes were not specified and multiple outcomes were examined without methods to control for multiplicity increasing risk of bias. Four patients (14.8%) were excluded increasing risk of attrition bias. Study was not powered to determine differences in outcomes.

Abbreviations: ACR50 = 50% improvement in the American College of Rheumatology criteria; BMD = bone mineral density; BMI = bod mass index; DMD = Duchenne Muscular Dystrophy; DXA = dual x-ray absorptiometry; ESRD = end-stage renal disease; MC = multicenter; MD = mean difference; NR = not reported; NS = not significant; OL = open-label; RA = rheumatoid arthritis; RCT = randomized clinical trial; SD = standard deviation; yrs = years.

Table 1. Pharmacology and Pharmacokinetic Properties.[1,10]

Parameter	
Mechanism of Action	Corticosteroid prodrug which has anti-inflammatory and immunosuppressant properties. The exact mechanism in patients with Duchenne muscular dystrophy is unclear.
Oral Bioavailability	Not reported; area under the curve is unchanged upon administration with food
Distribution and Protein Binding	Protein binding = 40% Exact volume of distribution is unknown
Elimination	68% excreted unchanged in urine 18% metabolized
Half-Life	Half-life of approximately 1.17 to 2.4 hours. Elimination is almost complete by 24 hours after a single dose.
Metabolism	Converted to the active metabolite, 21-des-deflazacort by esterase Metabolized via CYP3A4 and p-glycoprotein

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Appendix 1: Prescribing Information Highlights

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

EMFLAZA (deflazacort) tablets, for oral use
EMFLAZA (deflazacort) oral suspension
Initial U.S. Approval: 2017

----------INDICATIONS AND USAGE----------
EMFLAZA is a corticosteroid indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients 5 years of age and older (1)

----------DOSAGE AND ADMINISTRATION----------
- The recommended once-daily dosage is approximately 0.9 mg/kg/day administered orally (2.1)
- Discontinue gradually when administered for more than a few days (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
- Tablets: 6 mg, 18 mg, 30 mg, and 36 mg (3)
- Oral Suspension: 22.75 mg/mL (3)

----------CONTRAINDICATIONS----------
Hypersensitivity to deflazacort or any of the inactive ingredients in EMFLAZA (4)

----------WARNINGS AND PRECAUTIONS----------
- *Alterations in Endocrine Function*: Hypothalamic-pituitary-adrenal axis suppression, Cushing's syndrome, and hyperglycemia can occur; Monitor patients for these conditions with chronic use of EMFLAZA (2.2, 5.1)
- *Immunosuppression and Increased Risk of Infection:* Increased risk of new, exacerbation, dissemination, or reactivation of latent infections, which can be severe and at times fatal; Signs and symptoms of infection may be masked (5.2)
- *Alterations in Cardiovascular/Renal Function:* Monitor for elevated blood pressure and sodium, and for decreased potassium levels (5.3)
- *Gastrointestinal Perforation:* Increased risk in patients with certain GI disorders; Signs and symptoms may be masked (5.4)
- *Behavioral and Mood Disturbances:* May include euphoria, insomnia, mood swings, personality changes, severe depression, and psychosis (5.5)
- *Effects on Bones:* Monitor for decreases in bone mineral density with chronic use of EMFLAZA (5.6)
- *Ophthalmic Effects*: May include cataracts, infections, and glaucoma; Monitor intraocular pressure if EMFLAZA is continued for more than 6 weeks (5.7)
- *Vaccination:* Do not administer live or live attenuated vaccines to patients receiving immunosuppressive doses of corticosteroids (5.8)
- *Serious Skin Rashes:* Discontinue at the first sign of rash, unless the rash is clearly not drug related (5.9)

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥ 10% for EMFLAZA and greater than placebo) are Cushingoid appearance, weight increased, increased appetite, upper respiratory tract infection, cough, pollakiuria, hirsutism, central obesity, and nasopharyngitis (6.1)

----------DRUG INTERACTIONS----------
- Moderate or strong CYP3A4 inhibitors: Give one third of the recommended dosage of EMFLAZA (7.1)
- Avoid use of moderate or strong CYP3A4 inducers with EMFLAZA, as they may reduce efficacy (7.1)

To report SUSPECTED ADVERSE REACTIONS, contact Marathon Pharmaceuticals, LLC at 1-866-562-4620 or DrugSafety@propharmagroup.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 02/2017

Appendix 2: Literature search

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

1	deflazacort.mp.	527
2	limit 1 to (english language and humans)	377
3	limit 2 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)	155

Appendix 3. 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.

Approval Criteria		
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
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.

Approval Criteria		
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*

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

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.

Author: Sarah Servid, Pharm.D.
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*