

Drug Class Literature Scan: Drugs for Duchenne Muscular Dystrophy

Date of Review: September 2019

Date of Last Review: July 2017

Literature Search: 01/01/17 – 06/14/19

Current Status of PDL Class:

See [Appendix 1](#).

Conclusions:

- Two high-quality systematic reviews were identified which evaluated pharmacologic treatment for Duchenne muscular dystrophy (DMD).^{1,2}
- Current evidence demonstrates no difference in functional outcomes for eteplirsen compared to placebo.^{1,2} Evidence is significantly limited by high risk of bias and small sample sizes. There is no new clinical efficacy or safety evidence that would change current policy for eteplirsen.
- Deflazacort received an expanded FDA approval for children from 2 to 5 years of age.³ Labeling was also updated to recommend administration of all routine immunizations prior to initiation of treatment with deflazacort.³

Recommendations:

- Update prior authorization (PA) criteria to include updated FDA-approved ages and assessment of immunization status prior to initiation of treatment with deflazacort.

Summary of Prior Reviews and Current Policy

- 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.⁴ 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 20.⁵ Only 25% of patients remain ambulatory by age 16.⁶
- There is currently no curative treatment for DMD, and therapy focuses on improving symptoms, enhancing quality of life, and decreasing disease progression. Guidelines from the American Academy of Neurology currently recommend either deflazacort or prednisone as first-line treatment in children to improve muscle and pulmonary function and reduce risk of scoliosis.^{5,7}
- Therapies FDA approved for treatment of DMD were previously reviewed by the Pharmacy and Therapeutics (P&T) Committee in July 2017 and include eteplirsen and deflazacort. A previous evaluation of deflazacort found insufficient evidence to evaluate differences in efficacy or safety between deflazacort and other corticosteroids for DMD or other conditions. Evidence was limited by small sample sizes, lack of reported methodology and outcomes, and inadequate data in a United States population of patients. An evaluation of eteplirsen found insufficient evidence that eteplirsen is associated with any clinical change in symptoms or functional status for patients with DMD.

- Prior authorization (PA) is currently required for eteplirsen and deflazacort to ensure medically appropriate use (see **Appendix 1**). Prednisone is available without PA.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this literature scan is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

A 2017 drug review conducted by the OHSU Drug Effectiveness Review Project assessed evidence for eteplirsen efficacy and safety.¹ Evidence included 3 poor quality phase 1/2 trials of eteplirsen administered intramuscularly (n=7) or intravenously (n=31).¹ Early phase 1/2 trials demonstrated no consistent significant dose response in dystrophin expression or the North Star Ambulatory Assessment for muscle function.¹ Randomized, placebo-controlled data is limited to 12 patients administered eteplirsen 30 or 50 mg/kg over 24 weeks.¹ After 24 weeks, all patients entered an open-label treatment phase. Outcomes included the 6-minute walk test and level of dystrophin production evaluated via muscle biopsy. At 24 weeks, there was no significant difference in the 6-minute walk test between placebo and eteplirsen.¹ Results for dystrophin production upon biopsy were conflicting depending on the method of analysis. Randomized data was significantly limited by differences in baseline characteristics between groups and variable outcome assessment measures.¹ Open-label, uncontrolled data was further limited by use of a historical control as a comparator and risk for motivation bias and coaching which can bias outcomes in favor of treatment.¹

Because initial analysis of dystrophin positive fibers by western blot were oversaturated and uninterpretable, the manufacturer worked with the FDA to improve analyses for dystrophin production.¹ Repeat biopsies at week 180 were analyzed by western blot (which evaluates amount of dystrophin) and immunohistochemistry (which evaluates localization of dystrophin in tissue).¹ Western blot analyses demonstrated an average dystrophin level that was 0.93% of the normal protein level in healthy patients and immunohistochemistry analyses demonstrated that number of muscle fibers producing any dystrophin was increased from 1.1% at baseline to 17.4% at Week 180.¹ Dystrophin analyses were significantly limited by collection of 180-week biopsies from different muscle sites, lack of baseline values, and storage of control samples for 3 years with risk for protein degradation prior to analysis.¹ Due to these limitations, FDA medical reviewers concluded that dystrophin production was not interpretable as a categorically different result.¹

Similar results were noted in a high quality systematic review and meta-analysis which examined effect of exon skipping drugs on functional outcomes (6-minute walk test and North Star Ambulatory Assessment) in patients with DMD.² The systematic review identified only a single trial of eteplirsen compared to placebo.² Overall, authors concluded that there is no evidence that exon-skipping drugs are effective in DMD based on currently available data.²

After review, 2 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).^{8,9}

New Guidelines:

No new high quality guidelines were identified.

New Formulations and Indications:

No new formulations were identified.

Since initial approval, deflazacort has received an expanded indication in patients 2 to 5 years of age.³ It was previously approved in patients at least 5 years of age, and this expanded approval was based on efficacy and safety in patients 5 years and older with DMD.³

New FDA Safety Labeling:

Labeling for deflazacort was updated to recommend administration of all routine immunizations prior to initiation of treatment with deflazacort. Live-attenuated or live vaccines should be administered at least 4 to 6 weeks prior to starting therapy.³

Randomized Controlled Trials

A total of 8 citations were manually reviewed from the initial literature search. After further review, all studies were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).¹⁰⁻¹⁴

References:

1. Blazina I, Lazur, B., McDonagh, M., Woods, T., & Harrod, C. Eteplirsen (Exondys 51): Evidence, research pipeline, and management strategies. Portland, OR: Center for Evidence-based Policy and Pacific Northwest Evidence-based Practice Center, Oregon Health & Science University. 2017.
2. Shimizu-Motohashi Y, Murakami T, Kimura E, et al. Exon skipping for Duchenne muscular dystrophy: a systematic review and meta-analysis. *Orphanet J Rare Dis.* 2018;13(1):93.
3. Emflaza (deflazacort) [package insert]. Northbrook, IL: Marathon Pharmaceuticals, LLC. June 2019.
4. Deflazacort Medical Review. US Food and Drug Administration Center for Drug Evaluation and Research. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208684,208685Orig1s000TOC.cfm.
5. Carson S, Driver R, and Harrod C. Emflaza (deflazacort) for children with Duchenne muscular dystrophy: Comparative effectiveness versus prednisone. In. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University. April 2017.
6. Deflazacort Summary Review. US Food and Drug Administration Center for Drug Evaluation and Research. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208684,208685Orig1s000TOC.cfm.
7. Gloss D, Moxley RT, 3rd, Ashwal S, et al. Practice guideline update summary: Corticosteroid treatment of Duchenne muscular dystrophy: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology.* 2016;86(5):465-472.
8. Randeree L, Eslick GD. Eteplirsen for paediatric patients with Duchenne muscular dystrophy: A pooled-analysis. *Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia.* 2018;49:1-6.
9. Shieh PB, McIntosh J, Jin F, et al. Deflazacort versus prednisone/prednisolone for maintaining motor function and delaying loss of ambulation: A post HOC analysis from the ACT DMD trial. *Muscle Nerve.* 2018;58(5):639-645.
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11. Guglieri M, Bushby K, McDermott MP, et al. Developing standardized corticosteroid treatment for Duchenne muscular dystrophy. *Contemporary clinical trials*. 2017;58:34-39.
12. Jensen L, Petersson SJ, Illum NO, et al. Muscular response to the first three months of deflazacort treatment in boys with Duchenne muscular dystrophy. *Journal of musculoskeletal & neuronal interactions*. 2017;17(2):8-18.
13. Kinane TB, Mayer OH, Duda PW, et al. Long-Term Pulmonary Function in Duchenne Muscular Dystrophy: Comparison of Eteplirsen-Treated Patients to Natural History. *Journal of neuromuscular diseases*. 2018;5(1):47-58.
14. McDonald CM, Henricson EK, Abresch RT, et al. Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. *Lancet*. 2018;391(10119):451-461.

Appendix 1: Current Preferred Drug List

<u>Generic</u>	<u>Brand</u>	<u>Route</u>	<u>Form</u>	<u>PDL</u>
deflazacort	EMFLAZA	PO	ORAL SUSP	
deflazacort	EMFLAZA	PO	TABLET	
eteplirsen	EOXNDYS 51	IV	VIAL	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) 1946 to June Week 2 2019

1 deflazacort.mp.	505
2 eteplirsen.mp.	78
3 exp Muscular Dystrophies/	25480
4 1 or 2	582
5 3 and 4	161
6 limit 5 to (english language and humans)	143
7 limit 6 to yr="2017 -Current"	48
8 limit 7 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or equivalence trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	8

Appendix 3: Key Inclusion Criteria

Population	Patients with DMD
Intervention	Deflazacort or eteplirsen
Comparator	Other active comparators or placebo
Outcomes	Symptom, disability or functional improvement Mechanical ventilation Disease progression Morbidity or mortality
Setting	Outpatient

Appendix 4: 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 (billed as a pharmacy or physician administered claim)

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.

Approval Criteria

2. Is the drug being used to treat an OHP-funded condition AND is the requested treatment funded by the OHP for that condition?

Note: Treatments referenced on an unfunded line of the prioritized list (<http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Prioritized-List.aspx>) are not funded by the 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

5. Is the request for deflazacort?

Yes: Go to #6

No: Go to #98

6. Is the patient \geq 5-2 years of age?

Yes: Go to #7

No: Pass to RPh. Deny; medical appropriateness.

7. Has the patient received, or have contraindications to, all routine immunizations recommended for their age?

Note: Routine vaccinations for patients at least 2 years of age typically include hepatitis B, hepatitis A, diphtheria, tetanus, pertussis, pneumococcal conjugate, inactivated poliovirus, influenza, measles, mumps, rubella, and varicella.

Yes: Go to #8

Document physician attestation of immunization history.

No: Pass to RPh. Deny; medical appropriateness.

Approval Criteria

8. Does the patient have a documented contraindication or intolerance to oral prednisone that is not expected to crossover to deflazacort?	<p>Yes: Approve for up to 12 months.</p> <p>Document contraindication or intolerance reaction.</p>	<p>No: Pass to RPh. Deny; medical appropriateness.</p> <p>Recommend trial of another oral corticosteroid.</p>
9. Does the patient have a diagnosis of Duchenne Muscular Dystrophy with one of the following genetic mutations amenable to exon 51 skipping: <ul style="list-style-type: none"> • 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? 	<p>Yes: Go to #109</p> <p>Document genetic testing.</p>	<p>No: Pass to RPh, Deny; medical appropriateness.</p>
10. Has the patient been on a stable dose of corticosteroid for at least 6 months?	<p>Yes: Go to #110</p>	<p>No: Pass to RPh. Deny; medical appropriateness.</p>
11. Has baseline functional assessment been evaluated using a validated tool such as the 6-minute walk test or North Star Ambulatory Assessment?	<p>Yes: Document baseline functional assessment and approve for up to 6 months</p>	<p>No: Pass to RPh. Deny; medical appropriateness.</p>

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?	<p>Yes: Approve for up to 6 months</p> <p>Document functional status.</p>	<p>No: Pass to RPh, Deny; medical appropriateness.</p>
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P&T/DUR Review:
Implementation:

[09/19](#); 11/17; 07/17 (SS)
[TBD](#); 1/1/18; 9/1/17