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Drug Class Update with New Drug Evaluation: Duchenne Muscular Dystrophy

Date of Review: February 2021

Date of Last Review: June 2020
Dates of Literature Search: 01/01/2020-11/12/2020
Brand Name (Manufacturer): Viltepso® (NS Pharma)
Dossier Received: yes

Generic Name: viltolarsen

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The purpose of this update is to evaluate place in therapy for viltolarsen, a new targeted therapy for Duchenne muscular dystrophy (DMD). Viltolarsen is the second therapy approved for DMD in patients with mutations amenable to exon 53 skipping.

Research Questions:
1. What is the comparative efficacy or effectiveness of therapies for DMD?
2. What is the comparative safety of therapies for DMD?
3. Is viltolarsen safer or more effective than currently available agents for the treatment of patients with DMD?
4. Are there any subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) that would benefit or be harmed from drugs for DMD?

Summary of Prior Reviews and Current Policy
Therapies FDA approved for treatment of DMD (eteplirsen, golodirsen, and deflazacort) were previously reviewed by the Pharmacy and Therapeutics (P&T) Committee in June 2020. 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. Current evidence demonstrates no difference in functional outcomes for eteplirsen or golodirsen compared to placebo. Evidence is significantly limited by high risk of bias and small sample sizes. Prior authorization (PA) is currently required for deflazacort and all target therapies for DMD to ensure medically appropriate use (see **Appendix 5**). Prednisone is available without PA.

Conclusions:
- There is no new comparative efficacy or safety data for golodirsen or eteplirsen. The required post-marketing studies to verify and describe the clinical efficacy of eteplirsen and golodirsen have not yet been completed.

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- A systematic review conducted by the Drug Effectiveness Review Project (DERP) evaluated efficacy and safety of deflazacort compared to prednisone. 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.[1] Similarly, there is insufficient evidence to evaluate comparative differences in adverse effects between deflazacort and prednisone. Compared to prednisone, deflazacort may be associated with less weight gain but increased risk for cataracts and fractures.[1] 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.[1]
- There is insufficient evidence that use of viltolarsen in patients with DMD mutations amenable to exon 53 skipping has any impact on symptoms, muscle or pulmonary function, quality of life, or disease progression. Efficacy trials comparing viltolarsen to placebo have not yet been completed.
- Viltolarsen 80 mg/kg weekly was approved based on a phase 2 trial with high risk of bias, which demonstrated a slight improvement in dystrophin protein over 24 weeks compared to baseline (mean improvement of 5.3% of normal [SD 4.5; 95% CI 3.4 to 7.4]).[2,3] The functionality of the truncated dystrophin protein produced as a result of viltolarsen treatment has not been determined and may vary depending on the type of inherited mutation. It is not known if improvement in dystrophin correlate to clinical outcomes, and there is no consensus on the minimum amount of dystrophin that may result in a clinical improvement.
- There is insufficient evidence regarding long-term safety of viltolarsen. Evidence is limited by the small population of patients which have received viltolarsen. Only 16 patients had been prescribed viltolarsen for more than 12 months prior to approval by the Food and Drug Administration (FDA).[2] Like golidersen, viltolarsen labeling includes warnings for renal adverse events based on data from animal studies. Because viltolarsen is administered intravenously weekly, like other targeted therapies for DMD, there is possible risk of serious infections related to use of indwelling catheters, particularly in patients receiving chronic corticosteroids.

Recommendations:

- Prior authorization (PA) criteria for DMD updated to include viltolarsen to ensure medically appropriate use.
- After evaluation of costs in executive session, no changes were made to the PDL.

Background:

Duchenne muscular dystrophy (DMD) is a rare X-linked genetic disorder caused by the absence of a functional dystrophin protein. DMD primarily affects males and is the most common type of muscular dystrophy with an estimated worldwide prevalence of 1.7 to 4.2 in 100,000 patients.[4] In the United States, it's estimated that Duchenne and Becker muscular dystrophies may affect 1.4 to 2 in 10,000 males ages 5 to 9 years,[2,4] and the estimated incidence of new DMD patients is 1 in approximately 5000 male births.[5] Patients with DMD experience progressive muscle deterioration leading to loss of ambulation and decreased muscle strength. Long-term complications include respiratory failure, dilated cardiomyopathy, arrhythmias, and increased risk for thrombotic events. In many patients, these complications can lead to wheelchair dependence by age 12 and death at an early age.[4] In a recent systematic review assessing median survival of patients with DMD, improved trends in survival over time were identified which authors attributed to improvements in care, including use of ventilator support, leading to a decrease in respiratory-associated deaths in this population.[6] Age of death in patients in earlier decades (e.g., 1960s-1970s), was significantly earlier than age of death for patients who died in more recent decades.[6] The pooled median survival was 29.9 years (95% CI 26.5 to 30.8) in patients with ventilator support compared to 19 years (95% CI 18 to 20.9) in patients without ventilator support.[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 recommend initiation of corticosteroids, either deflazacort or prednisone, as first-line treatment for ambulatory children with a decline in motor function to delay loss of ambulation, preserve pulmonary function, and reduce risk of scoliosis.[4,7] Corticosteroids are

often continued if patients become non-ambulatory, though the continued benefits are less clear with progressive disease.[4] 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]

Recent new therapies approved for DMD include targeted, exon-skipping therapies. The goal of these therapies is to modify mRNA splicing and increase the amount of dystrophin protein in cells, thereby correcting the underlying disease process. Using this mechanism, a truncated dystrophin protein is formed. While preclinical animal studies indicate truncated dystrophin can be functional, the level of function associated with the truncated protein is unknown and may vary depending on the inherited mutation.[8] Therapies are FDA approved for specific mutations that are amenable to exon skipping. Eteplirsen was FDA approved in 2016 for DMD with mutations amenable to exon 51 skipping. Approximately 13% of patients with DMD are thought to have mutations amenable to exon 51 skipping.[9] In the past year, golodirsen and, more recently, viltolarsen were FDA approved for patients with mutations amenable to exon 53 skipping. Mutations amenable to exon 53 skipping are thought to represent about 8% of the DMD population (approximately 1200 patients in the United States).[10] Both therapies have the same mechanism of action and are administered as weekly intravenous infusions.

These therapies have been approved based on the surrogate marker of dystrophin protein. While eteplirsen and golodirsen have shown a slight increase in dystrophin (<1% of normal dystrophin levels), the impact of these therapies on clinical outcomes had not been demonstrated in randomized controlled trials.[11,12] In the trial used for eteplirsen approval (n=12), there was no difference observed in the 6-minute walk test at 24 or 48 weeks compared to placebo. While subsequent follow-up studies have evaluated pulmonary, cardiac, and muscle function in this population, they are limited by their single-arm observational design, small sample size, and lack of comparator groups or comparison to historical control.[13-16] Similarly, there are no published, placebo-controlled studies evaluating functional outcomes with golodirsen, and FDA review of available clinical outcomes identified no substantial difference from natural history data.[10] Confirmatory post-marketing, randomized trials have yet to be completed for either therapy.

Targeted exon skipping therapies for DMD have been FDA-approved based on a surrogate marker of dystrophin production. It is unclear whether increases in dystrophin protein level in patients with DMD correlate to clinical outcomes, and there is currently no consensus on the minimum change in dystrophin level that may result in a clinical improvement. Available thresholds cited in the literature are currently based on expert opinion, and evidence has yet to correlate improved dystrophin levels in patients with DMD with any clinical outcomes. An FDA analysis evaluating the change in 6MWT per year and dystrophin level associated with golodirsen failed to demonstrate a positive correlation (R=0.14), indicating that increases in a truncated dystrophin protein may not be an adequate surrogate marker for functional improvement.[10] In untreated patients with DMD, documented dystrophin levels typically range from 0 to 0.4% of normal healthy patients.[17] Experts suggests that dystrophin levels less than 3% of normal are typically associated with a phenotype of DMD.[17] Some experts suggest that very minimal improvements in dystrophin level may constitute a beneficial change while others suggest that dystrophin levels at 10-20% of normal would likely correlate to clinically significant changes in muscle symptoms or function.[17,18] In patients with Becker muscular dystrophy, a less severe form of the muscular dystrophy, dystrophin protein levels are on average 80% of normal.[17]

Clinically important outcomes in DMD include morbidity, mortality, disease progression, motor function, and improvements in motor, pulmonary, or cardiac symptoms. There are multiple methods used assess motor function and strength in patients with DMD including timed functional tests scoring tools. For example, the North Star Ambulatory Assessment (NSAA) is a 17-item scale designed for patients able to ambulate at least 10 meters (total score range 0 to 34). It evaluates various functional assessments including standing, hopping, climbing stairs, and rising from the floor. Individual items are rated on a 0 to 2 scale based on ability to perform the test normally (2), able to perform the test with modifications or assistance (1), and inability to perform the test (0). The minimum clinically important difference in NSAA score has not been established. Other standard timed functional tests include time to climb 4 stairs, time to walk 10

meters, time required to stand from a prone position, and the 6 minute walking test (6MWT) which evaluates distance traveled in 6 minutes. 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.[16,19,20] The minimum clinically important difference in the 6MWT for patients with DMD is approximately 30 meters.[21] 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.[22] The NSAA is generally considered a more comprehensive measure of functional status compared to other functional outcomes, but score is often very dependent on patient effort.[17] Pulmonary function is often evaluated during clinical trials using spirometry. In patients with DMD, current evidence demonstrates a gradual decline in pulmonary function tests beginning around 5 years of age (about 4-7% per year of percent predicted forced vital capacity [FVC] and peak expiratory flow [PEF]).[23,24] However, there is currently only limited data to correlate decline in percent predicted FVC or PEF to thresholds for clinical outcomes such as need for mechanical ventilation or airway clearance.[23]

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 review 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.

Systematic Reviews:

A high quality systematic review conducted by the Drug Effectiveness Review Project (DERP) evaluated efficacy and safety of prednisone compared to deflazacort.[1] This systematic review was an update of a 2017 review. In the original review, 4 comparative RCTs were identified. This update identified several new observational studies and one systematic review, but no new RCTs. Evidence from RCTs was significantly limited by poor methodological quality and inconsistency across studies.[1] Limitations included incomplete outcome reporting, high attrition, and unclear randomization and allocation concealment methods.[1] Studies were of generally of small sample size (18 to 196 patients) and of short duration (3 months to 2 years).[1] While deflazacort has an FDA-approved indication for patients at least 2 years of age, trials only included patients over 5 years of age.[1] Evidence for functional outcomes was graded as very low quality indicating no confidence in the direction of effect.[1] One small trial (n=34) reported improved motor function index score with deflazacort compared to prednisone at 18 months (18.1% vs. 15%), but no difference in functional motor outcomes upon follow-up at 24 months.[1] Two trials reported no difference between deflazacort and prednisone in muscle strength from baseline to 3 to 12 months.[1] Similarly, all outcomes pertaining to differences in adverse effects were graded as very low quality due to methodological limitations. Four studies reported less weight gain with deflazacort compared to prednisone. Average differences in weight from baseline are reported in **Table 1**. Two RCTs noted increased risk for cataracts with deflazacort with differences of 6.6% versus 4.4% and 36% versus 3%, respectively.[1]

Table 1. Average weight change from baseline reported in RCTs[1]

Study	Duration	Deflazacort	Prednisone	Statistical reporting
Griggs et al N=196	12 months	5.05 kg; 95% CI, 4.08 to 6.01	8.45 kg; 95% CI, 7.41 to 9.49	P<0.001
Bonifati et al. N=18	12 months 24 months	2.17 kg (variance not reported) 4.6 kg (variance not reported)	5.08 kg (variance not reported) 8.7 kg (variance not reported)	P<0.05 P<0.05
Karimzadeh et al N=34	12 months 18 months	13.0% (variance not reported) 21.7% (variance not reported)	21.7% (variance not reported) 32.0% (variance not reported)	P=0.001 P=0.046
Reitter, 1995; Dubowitz, 2000 N=100	24 months	Not reported	Not reported	Statistical significant difference reported only descriptively

Seven observational trials which compared deflazacort to prednisone were described in the DERP report. All had significant risk for selection bias related to availability of deflazacort compared to prednisone, differences in baseline characteristics between groups, lack of disclosure for study funding, and small sample sizes.[1] For example, several trials had a higher daily doses of deflazacort compared to prednisone dose which may account for some differences between groups.[1] Because of these substantial differences in baseline characteristics between groups, it significantly limits confidence in findings from these studies.

Efficacy Outcomes

- Four trials reported age of ambulatory loss as a functional outcome with inconsistency between studies. Two studies reported no difference between deflazacort and prednisone, and two studies, both evaluating data from the Cooperative International Neuromuscular Research Group Duchenne Natural History Study (CINRG DNHS) dataset, found improvement in patients treated with deflazacort compared to prednisone by a median of 2.7 years (13.9 vs. 11.2; p< 0.001 and 14.0 ± 0.20 vs. 11.3 ± 0.42; p=0.01).[1]
- Data for other motor function outcomes was mixed not reported consistently for all outcomes across studies.

Safety Outcomes

- Five of the 6 studies evaluating weight gain reported similar changes in weight between groups.[1] Only one trial evaluated statistical differences in weight and found less weight gain associated with deflazacort compared to prednisone.[1] However, in the same study no differences in BMI were observed which authors attributed to a significantly shorter stature in patients treated with deflazacort.[1] This observational data conflicts with differences in weight observed in RCT. However, it is possible that differences in results may be explained by variability in deflazacort and prednisone dose in observational studies, limited statistical analysis of weight-related outcomes, and lack of long-term outcomes in RCTs.[1]
- Of the 4 observational studies evaluating cataracts, 2 identified a statistically significant increased risk of cataracts with deflazacort compared to prednisone (OR 2.4; 95% CI 1.5 to 4.5 and 29% vs. 5%, respectively).[1] Two studies reported numerically higher incidence of cataracts with deflazacort compared to prednisone, though statistical significance was not reported.[1]
- Adverse effects related to growth delay were mixed with 2 studies noting increased risk of growth delay associated with deflazacort compared to prednisone and 2 studies noting no difference between treatments.[1]
- In one retrospective analysis, deflazacort was associated with an evaluated fracture risk compared to prednisone. The time to first fracture was shortest with deflazacort (mean 5.9 years; 95% CI 4.5 to 7.3; *p=0.*03).[1] Overall fracture incidence rate in patients with DMD was 682 per 10000 patient-years (95% CI 579-798) and was highest in patients treated with daily deflazacort (1366.6 per 10000 patient-years; 95% CI 796.1-2188.0).[25]

After review, one systematic review was excluded due to poor quality (e.g., did not meet AMSTAR II criteria).[5]

New Guidelines:
No new high quality guidelines were identified since the last review.

New Formulations or Indications:
No new formulations were identified.

New FDA Safety Alerts:
No new safety alerts were identified.

Randomized Controlled Trials:
A total of 16 citations were manually reviewed from the initial literature search. None of the identified studies met quality inclusion criteria. All citations 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). Key inclusion criteria for RCTs are listed in **Appendix 4**. The phase 2 RCT evaluating efficacy of viltolarsen was included in the new drug evaluation below as it was the primary trial used for FDA-approval.

NEW DRUG EVALUATION:
See **Appendix 3** 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.

Clinical Efficacy:
Viltolarsen 80 mg/kg weekly was FDA-approved for DMD based on a phase 2, dose-finding trial with high risk of bias (**Table 4**).[3] A second phase 2, dose-finding trial conducted in Japan remains unpublished, and data from this study was not used for FDA approval due to lack of adequate methods for dystrophin measurment.[2] The trial used for FDA-approval enrolled 16 patients who were randomized to low (40mg/kg) or high (80mg/kg) dose viltolarsen for 4 weeks.[3] A placebo group was included for safety outcomes only for the first 4 weeks. Patients were enrolled in a 20 week open-label extension phase with either 40 or 80 mg/kg viltolarsen following the randomized 4-week safety period.[3] The study had high risk of bias, primarily due to the lack of placebo comparator and open-label design after 4 weeks. Laboratory outcomes were reported as pre-specified, but results were available for only 3 of the 6 functional outcomes (those that had demonstrated statistical significance). Patients enrolled in the phase 2 trial were ambulatory and able to complete all baseline functional assessments limiting applicability in patients with severe disease.[3]

The primary efficacy outcome was change in dystrophin production evaluated by Western blot analysis.[3] Western blot analysis provides a semi-quantitative assessment of dystrophin production by comparing muscle biopsy samples to a standard curve of dystrophin generated from biopsies collected from a range of patients with varying dystrophin levels (patients with DMD to normal controls). Results are reported as a percent of normal dystrophin levels. At baseline, the mean dystrophin level was 0.6% of normal by Western blot.[2] The primary outcome was supported by analysis of dystrophin using 3 other methods: dystrophin mRNA splicing on reverse transcription-polymerase chain reaction (RT-PCR), dystrophin protein production by mass spectrometry (MS), and dystrophin

localization by immunofluorescence (IF) staining.[3] The FDA recommends that IF staining and RT-PCR be used as qualitative assessments only and are not recommended to make conclusions regarding dose or efficacy.[2] Upon analysis by Western blot at 24 weeks, patients treated with viltolarsen demonstrated a mean improvement in dystrophin from baseline of 5.3% (SD 4.5; 95% CI 3.4 to 7.4) to 5.4% (SD 2.4; 95% CI 1.6 to 9.0%) for patients treated with 80 and 40 mg/kg, respectively.[2,3] FDA approval was for 80 mg/kg weekly. A dose response was not observed with analysis of dystrophin by Western blot, but there was a numerically higher (though not statistically significant) dose response upon analysis by MS (mean difference of 3.7% vs. 1.5% of normal for 80 and 40 mg/kg, respectively, p=0.16 between groups).[2] In general, all secondary analysis methods reported consistent direction of effect with regard to dystrophin production.[2] Patients who demonstrated higher improvement on Western blot analysis also had consistent outcomes when using other analytical methods to evaluate dystrophin levels.[2]

Evaluation of dystrophin in patients treated with golodirsen and eteplirsen resulted in changes in dystrophin of that were less than 1% of normal.[11,26] While viltolarsen had a mean improvement of 5.3% to 5.4% of normal, it is difficult to make comparisons between trials due to differences in populations, genotypes, and variability in methods used for evaluation of dystrophin. For example, it is likely that genotype impacts disease progression and may be a possible factor in dystrophin production for patients amenable to exon 51 versus 53 skipping. In patients amenable to exon 53 skipping, patients enrolled in the trial for golodirsen were slightly older (mean 8.2 years) compared to viltolarsen trials (7.4 years).[3,26]

While a comparison of functional outcomes was performed versus historical controls, use of historical controls in this population has significant limitations and should not be used for evaluation of efficacy. Patients enrolled in the clinical trial were not matched to historical controls and relevant clinical data regarding time and age of diagnosis, corticosteroid dose, ventilator support, cardiac or pulmonary function, and data on other non-pharmacologic therapy was unavailable for historical controls.[3] Additionally, historical control patients had worse mean functional outcomes at baseline including a longer 6MWT, longer time to stand from supine, time to climb 4 stairs, and higher NSAA score.[3] This may be indicative of more severe or symptomatic disease for control patients which may bias results in favor of treatment. These potential confounding factors could have significant impact on disease progression or functional ability which increases risk of bias upon comparison to a historical control. Additional data are needed to confirm clinical benefit.

Similar to other targeted therapies for DMD, the clinical benefit of viltolarsen has yet to be determined. Currently available data indicate no clinical impact on disease progression, and available data are significantly limited by the open-label, non-controlled study design. Functional outcomes can be susceptible to expectation bias and coaching which significantly confounds the benefit when compared to historical disease progression. Additionally, it is unclear whether improvements in dystrophin correlate to clinical outcomes. There is currently no consensus on what difference in dystrophin may be clinically significant.

Clinical Safety:
At the time of FDA approval there were 32 patients exposed to viltolarsen, 16 of which had been on treatment for more 12 months.[2] During clinical trials there were no deaths, no discontinuations due to adverse events and only 2 patients experienced severe adverse events (respiratory tract infection and limb fracture).[2] The most common adverse events were upper respiratory infections, injection site reactions, cough, and pyrexia (**Table 2**).

Table 2. Adverse events occurring in more than 10% of patients receiving viltolarsen 80 mg/kg.[27]

Adverse event	Viltolarsen 80 mg/kg weekly (n=16)
Upper respiratory tract infection	10 (63%)
Injection site reaction	4 (25%)
Cough	3 (19%)
Pyrexia	3 (19%)
Contusion	2 (13%)
Arthralgia	2 (13%)
Diarrhea	2 (13%)
Vomiting	2 (13%)
Abdominal pain	2 (13%)
Ejection fraction decreased	2 (13%)
Urticaria	2 (13%)

Because viltolarsen is administered intravenously weekly, there is possible risk of serious infections related to use of indwelling catheters, particularly in patients receiving chronic corticosteroids.[2] This concern was first noted in an FDA review of post-marketing adverse events for eteplirsen and is a potential risk for all weekly intravenous treatments for DMD. In addition, like other oligonucleotide therapies for DMD, pre-clinical animal studies identified a potential risk for serious renal adverse events. While no renal adverse events were documented in clinical trials, renal monitoring is recommended prior to and during viltolarsen therapy.[27] Because serum creatinine may not accurately reflect renal function in patients with DMD, labeling recommendations include serum cystatin C, urine dipstick, and urine protein-to-creatinine ratio.[27] If persistent changes are noted, a referral to a pediatric nephrologist is recommended.

In the available clinical studies, only one patient (6.25%) was identified with anti-drug antibodies.[2] However, due to the sensitivity of the test used, false negatives could not be ruled out, and a post-marketing trial with improved sensitivity is required to validate these results.[2] Additional post-marketing requirements include an assessment of viltolarsen on QT prolongation, animal carcinogenicity studies, a placebo controlled trial over 48 weeks to establish efficacy (primary endpoint planned as time to stand), and surveillance for serious renal adverse events.[2]

Look-alike / Sound-alike Error Risk Potential: None identified.

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Functional or symptom improvement (motor, pulmonary, or cardiovascular)
2) Quality of life
3) Disease progression
4) Mortality
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Efficacy Endpoint:

1) Dystrophin protein production

Table 3. Pharmacology and Pharmacokinetic Properties.[27]

Parameter	
Mechanism of Action	Viltolersen binds to Exon 53 of the dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing and producing an internally truncated dystrophin protein
Oral Bioavailability	N/A (administered intravenously)
Distribution and Protein Binding	Vd = 0.3 L/kg at FDA approved dose (80mg/kg) 39-40% protein binding
Elimination	Excreted unchanged in the urine
Half-Life	2.5 hours
Metabolism	N/A

Abbreviations: kg= kilograms; L=liters; N/A = not applicable; Vd = volume of distribution

Table 4. 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.Clemens, et al. 2020.[3] FDA Summary Review[2] Phase 2, open-label, dose-comparison, MC, RCT	1. viltolarsen 80 mg/kg weekly 2. viltolarsen 40 mg/kg weekly 3. placebo 4 weeks Following 4 weeks participants were enrolled in a 20-week open label extension. Patients originally randomized to placebo were switched to viltolarsen.	Demographics: - Age: 7.4 yrs (SD 1.8) - White: 94% - BMI: 17.4-17.9 kg/m^2 - Time to run/walk 10 m: 5.93 s (SD 1.47) - Time to stand from supine: 4.44 s (SD 1.96) - 6MWT: 372.4 m (SD 78.6) - Time to climb 4 stairs: 3.61 s (SD 0.95) - NSAA: 24.3 (SD 5.4) Key Inclusion Criteria: - Age 4-9 yrs - DMD amenable to exon 53 skipping - Normal labs - Ambulatory without assistive devices - Able to complete baseline functional assessments - Stable steroid dose in prior 3 months Key Exclusion Criteria: - Acute illness 4 weeks before enrollment* - Symptomatic cardiomyopathy - Severe behavioral or cognitive problems - Surgery in prior 3 mo - HBV, HCV, HIV - Other medical findings which would impair assessment of study results or safety* *as assessed by site investigator	Part 1: ITT 1. 6 2. 6 3. 4 PP 1. 6 2. 5 3. 5 Part 2 1. 8 2. 8 Attrition 1. 0 2. 0	Primary Endpoint: Dystrophin production (by Western blot) at 24 wks 1. 5.9% (SD 4.5%); change from baseline: 5.3% (SD 4.5%); 95% CI 3.4 to 7.4% 2. 5.7% (SD 2.4%); change from baseline: 5.4% (SD 2.4%); 95% CI 1.6 to 9.0% Secondary Endpoints: Outcomes for functional assessments were reported graphically or at 25 weeks compared to historical control and should not be used to establish efficacy. Measures of variance were reported only graphically. Mean change in time to stand from supine Viltolarsen: -0.19s Historical Control: 0.74s P=0.04 * when evaluated as velocity results were NR with NS difference from historical controls Change in time to travel 10m (velocity) Viltolarsen: 0.23m/s Historical Control: -0.04m/s P=0.003 Change in time to travel 10m (reported graphically; results are approximate) Viltolarsen: -0.6s Historical control: 0.1s p=0.046 Change in time to climb 4 stairs, NSAA, and muscle strength not reported Difference from historical control: NS Change in 6MWT from baseline (25 wks) Viltolarsen: 28.9 m Historical control: -65.3 m P=0.047	NA for all	SAE 0% DC due to AE: 0% TEAE 1. 4 (67%) 2. 4 (80%) 3. 3 (60%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: High. Method of randomization not reported; no allocation concealment. An unblinded statistician performed randomization based on a permuted block design. Performance Bias: High. Open-label design without placebo comparison for all outcomes after 4 weeks. Lack of blinding increases risk of bias for effort-based functional assessments. Detection Bias: High. Laboratory assessors blinded to treatment group. Blinding of sample type (before vs. after therapy) was NR. Attrition Bias: Low. One patient randomized to vilitolarsen but received placebo for 4 weeks. All patients completed 24 weeks of treatment. Reporting Bias: Unclear. Primary results reported as specified. Results available for only 3 of 6 functional outcomes. No multiplicity testing for multiple outcomes. Other Bias: Unclear. Manufacturer was involved in study design; collection, management, analysis and interpretation of data; and preparation and review of the paper. **Applicability**: Patient: Patients were ambulatory and able to complete all baseline functional assessments. Patients with acute illness or cardiomyopathy were excluded limiting applicability in patients with severe disease. Baseline pulmonary function was not reported. Intervention: Intervention given as a 2nd line therapy to corticosteroids. Functional outcomes were not reported by dose and no dose response was observed upon analysis of dystrophin production by Western blot. Upon analysis by MS, there was a slightly higher (though not significant) improvement in dystrophin production with the FDA approved dose of 80 mg/kg compared to 40 mg/kg (3.7% vs. 1.5% of normal, respectively, p=0.16). Comparator: Lack of control group after 4 weeks limits conclusions regarding efficacy of treatment or long-term safety. Functional outcomes compared to historical control. No patient to patient matching occurred for historical control and important markers of disease progression were not reported including steroid dose, pulmonary function, and non-pharmacological therapy (e.g., physical therapy, assistive devices, ventilator support, etc).

								Outcomes: Primary outcome is a surrogate marker and correlation of functional outcomes with dystrophin levels is unclear. There is no agreement on what level of dystrophin may result in a clinically important difference. Setting: 5 sites in the United States and 1 site in Canada from December 2016 to August 2017.

Abbreviations [alphabetical order]: 6MWT = 6 minute walk test; AE = adverse events; ARR = absolute risk reduction; BMI = body mass index CI = confidence interval; DC = discontinuation; DMD = Duchenne muscular dystrophy; FDA = Food and Drug Administration; HBV = hepatitis B; HCV = hepatitis C; HIV = human immunodeficiency virus; ITT = intention to treat; MC = multicenter; mo = months; MS = mass spectrometry; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = non-significant; NSAA = North Star Ambulatory Assessment; PP = per protocol; RCT = randomized controlled trial; SAE = serious adverse events; SD = standard deviation; TEAE = treatment-emergent adverse events; wks = weeks; yrs = years

References:

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route
deflazacort	EMFLAZA	ORAL SUSP	PO
deflazacort	EMFLAZA	TABLET	PO
eteplirsen	EXONDYS-51	VIAL	IV
golodirsen	VYONDYS-53	VIAL	IV
viltolarsen	VILTEPSO	VIAL	IV

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to November 11, 2020

1	exp Muscular Dystrophy, Duchenne/	5572
2	limit 1 to (english language and humans)	4118
3	limit 2 to yr="2020"	95
4	limit 3 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")	16

Appendix 3: Prescribing Information Highlights

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

VILTEPSO (viltolarsen) injection, for intravenous use
Initial U.S. Approval: 2020

----------INDICATIONS AND USAGE----------
VILTEPSO 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 53 skipping. This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with VILTEPSO. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. (1)

----------DOSAGE AND ADMINISTRATION----------
- Serum cystatin C, urine dipstick, and urine protein-to-creatinine ratio should be measured before starting VILTEPSO. (2.1)
- Recommended dosage is 80 milligrams per kilogram of body weight once weekly. (2.2)
- Administer as an intravenous infusion over 60 minutes. (2.2, 2.4)
- If the volume of VILTEPSO required is less than 100 mL, dilution in 0.9% Sodium Chloride Injection, USP, is required. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 250 mg/5 mL (50 mg/mL) in a single-dose vial (3)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
Kidney Toxicity: Based on animal data, may cause kidney toxicity. Kidney function should be monitored; creatinine may not be a reliable measure of renal function in DMD patients. (5.1, 13.2)

----------ADVERSE REACTIONS----------
The most common adverse reactions (incidence ≥15% in patients treated with VILTEPSO) were upper respiratory tract infection, injection site reaction, cough, and pyrexia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact NS Pharma at 1-866 NSPHARM (1-866-677-4276) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 8/2020

Appendix 4: Key Inclusion Criteria

Population	Patients with Duchenne Muscular Dystrophy
Intervention	Drugs listed in Appendix 1
Comparator	Drugs listed in Appendix 1 or placebo
Outcomes	Function, symptoms, disease progression, quality of life, morbidity, mortality
Timing	Any duration
Setting	Outpatient

Drugs for Duchenne Muscular Dystrophy

Goal(s):

- Encourage use of corticosteroids which have demonstrated long-term efficacy.
- Restrict use of eteplirsen, golodirsen, 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:

- Targeted therapies for exon skipping (pharmacy or physician administered claims)
- 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/

Table 1. FDA Approved Indications for targeted therapies

Drug	Indication	Examples of amenable mutations (list is not all inclusive)
eteplirsen (Exondys 51®)	Duchenne muscular dystrophy with mutations amenable to exon 51 skipping	Deletion of exons 43 to 50; 45 to 50; 47 to 50; 48 to 50; 49 to 50; 50; or 52
golodirsen (Vyondys 53®)	Duchenne muscular dystrophy with mutations amenable to exon 53 skipping	Deletion of exons 42 to 52; 45 to 52; 47 to 52; 48 to 52; 49 to 52; 50 to 52; 52; or 54 to 58
Viltolarsen (Viltepso®)	Duchenne muscular dystrophy with mutations amenable to exon 53 skipping	Deletion of exons 42 to 52; 45 to 52; 47 to 52; 48 to 52; 49 to 52; 50 to 52; 52; or 54 to 58

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	

Approval Criteria		
2. Is the request for treatment of Duchenne Muscular Dystrophy?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness. Note: Therapies are not indicated for other forms of muscular dystrophy or other diagnoses.
3. Is the request for deflazacort?	**Yes:** Go to #4	**No:** Go to #7
4. Is the patient ≥ 2 years of age?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. 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, and at least 2 doses of measles, mumps, rubella, and varicella.	**Yes:** Go to #6 Document physician attestation of immunization history.	**No:** Pass to RPh. Deny; medical appropriateness.
6. Does the patient have a documented contraindication or intolerance to oral prednisone that is not expected to crossover to deflazacort? Note: deflazacort may be an option for patients with clinically significant weight gain associated with prednisone use.	**Yes:** Approve for up to 12 months. Document contraindication or intolerance reaction.	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of prednisone.
7. Is the request for continuation of treatment previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #8

Approval Criteria		
8. Is the request for an FDA-approved indication (Table 1)?	**Yes:** Go to #9 Document genetic testing.	**No:** Pass to RPh, Deny; medical appropriateness.
9. Is the request for golodirsen or viltolarsen?	**Yes:** Go to #10	**No:** Go to #12
10. Is the request for combination treatment with 2 or more targeted therapies (e.g., golodirsen and viltolarsen)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #11
11. Has the provider assessed baseline renal function as recommended in the FDA label? Golodirsen: documented glomerular filtration rate as evaluated by a 24 hour urine collection within the past 3 months Viltolarsen: Serum cystatin C, urine dipstick, and urine protein-to-creatinine within the past 3 months	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness.
12. Has the patient been on a stable dose of corticosteroid for at least 6 months or have documented contraindication to steroids?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness.
13. Has baseline functional assessment been evaluated using a validated tool (e.g., the 6-minute walk test, North Star Ambulatory Assessment, etc)?	**Yes:** Document baseline functional assessment and approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request for golodirsen or viltolarsen?	**Yes:** Go to #2	**No:** Go to #3

Renewal Criteria		
2. Has the provider assessed renal function? Golodirsen: Recommended monitoring includes proteinuria monthly and serum cystatin C every three months. If results are abnormal, a 24H urine collection should be performed. Viltolarsen: Recommended monitoring includes urine dipstick monthly, serum cystatin C every 3 months, and protein-to-creatine ratio every 3 months.	**Yes:** Go to #3	**No:** Pass to RPh, Deny; medical appropriateness.
3. 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:** Go to #4 Document functional status and provider attestation.	**No:** Pass to RPh, Deny; medical appropriateness.
4. Is there documentation based on chart notes of any serious adverse events related to treatment (e.g., acute kidney injury, infections, etc.)?	**Yes:** Go to #5	**No:** Approve for up to 6 months
5. Has the adverse event been reported to the FDA Adverse Event Reporting System (FAERS)?	**Yes:** Approve for up to 6 months Document provider attestation	**No:** Pass to RPh, Deny; medical appropriateness.

P&T/DUR Review: *2/21 (SS); 6/20; 09/19; 11/17; 07/17*
Implementation: *3/1/21; 7/1/20; 11/1/19; 1/1/18; 9/1/17*