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Drug Class Update with New Drug Evaluation: Drugs for Duchenne Muscular Dystrophy

Date of Review: June 2020

Generic Name: golodirsen

Date of Last Review: September 2019
Dates of Literature Search: 06/01/2019-3/10/2019
Brand Name (Manufacturer): Vyondys 53™ (Sarepta)
Dossier Received: yes

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

Purpose for Class Update:
To evaluate new comparative evidence for drugs for Duchenne muscular dystrophy (DMD) and place in therapy for golodirsen, an antisense RNA recently approved by the Food and Drug Administration (FDA).

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 golodirsen 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?

Conclusions:
- There is no new comparative efficacy or safety data for eteplirsen or deflazacort. The required post-marketing study to verify and describe the clinical efficacy of eteplirsen has not yet been completed.
- There is insufficient evidence that use of golodirsen 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.
- Golodirsen was approved based on an ongoing, single-arm, open-label, phase I/II trial which demonstrated a small improvement in dystrophin protein over 48 weeks (change of 0.9% of normal compared to baseline).[1] The functionality of the truncated dystrophin protein produced as a result of golodirsen treatment has not been determined and may vary depending on the type of inherited mutation. It is not known if improvement in dystrophin correlates 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 golodirsen. FDA labeling for golodirsen includes warnings for hypersensitivity reactions and renal adverse events.

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Recommendations:

- Update prior authorization criteria for DMD (**Appendix 5**).

Summary of Prior Reviews and Current Policy

- Therapies FDA approved for treatment of DMD (eteplirsen and deflazacort) were previously reviewed by the Pharmacy and Therapeutics (P&T) Committee in July 2017 and September 2019. 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 compared to placebo. Evidence is significantly limited by high risk of bias and small sample sizes.
- Prior authorization (PA) is currently required for eteplirsen and deflazacort to ensure medically appropriate use (see **Appendix 5**). Prednisone is available without PA.

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.[2,3] 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 before the age of 20.[2]

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 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.[2,4] Corticosteroids are often continued if patients become non-ambulatory, though the continued benefits are less clear with progressive disease.[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.[2] As the disease progresses, mechanical ventilation and spinal surgery may be used to improve pulmonary function and decrease pain from scoliosis and vertebral fractures.[2]

Recent new therapies approved for DMD include eteplirsen and golodirsen. 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 produced by golodirsen is unknown and may vary depending on the inherited mutation.[5] Eteplirsen was FDA approved in 2016 for DMD with mutations amenable to exon 51 skipping and golodirsen was FDA approved in 2019 for patients with mutations amenable to exon 53 skipping. Approximately 13% of patients with DMD are thought to have mutations amenable to exon 51 skipping.[6] There are currently 8 known mutations amenable to exon 53 skipping, which are thought to represent about 8% of the DMD population (approximately 1200 patients in the United States).[7] 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 clinical benefit of these therapies has not been established.[8,9] 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.[10-12] Confirmatory post-marketing, randomized trials have yet to be completed for eteplirsen.

In untreated patients with DMD, documented dystrophin levels typically range from 0 to 0.4% of normal healthy patients.[13] Experts suggests that dystrophin levels less than 3% of normal are typically associated with a phenotype of DMD.[13] It is unclear whether increases in dystrophin protein level in patients with DMD correlate to clinical outcomes. Similarly, the minimum change in dystrophin level that may result in a clinical improvement has not been established. 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.[13,14] In patients with Becker muscular dystrophy, a less severe form of the muscular dystrophy, dystrophin protein levels are on average 80% of normal.[13]

Efficacy outcomes that 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.[15] 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.[16-18] The minimum clinically important difference in the 6MWT for patients with DMD is approximately 30 meters.[15] 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.[13] 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.[19] 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.[13] 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.[15]

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:
No new high quality systematic reviews identified.

New Guidelines:
No new high quality guidelines were identified.

New Formulations or Indications:

No new formulations or indications 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. Articles were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), outcome studied (e.g., non-clinical), or other key inclusion criteria in **Appendix 4**. The phase I/II, open-label extension trial evaluating efficacy of golodirsen 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:
Golodirsen is an antisense oligonucleotide which is designed to bind mRNA encoding the dystrophin protein resulting in altered mRNA splicing and restoration of the reading frame during protein formation to create a truncated dystrophin protein. Golodirsen was approved through the accelerated approval pathway based on a single, ongoing, phase I/II study which demonstrated changes in dystrophin over 48 weeks in 25 males with DMD and dystrophin mutations amenable to exon 53 skipping (described below in **Table 3**).[1] The study was divided into 2 parts. Part 1 was a randomized, double-blind, placebo-controlled, 12 week, dose titration study to evaluate the safety and pharmacokinetics of golodirsen. Patients completing part 1 of the study were enrolled in part 2 to evaluate efficacy and safety of golodirsen. Part 2 is an ongoing, single-arm, open-label extension study to evaluate efficacy and safety over 144 weeks (2.8 years).[1] The primary biologic outcome was dystrophin protein levels (evaluated by Western blot analysis) at 48 weeks, and the primary efficacy outcome was change in 6MWT at 144 weeks.[1] Relevant clinical secondary outcomes included pulmonary function tests. Currently only data for biologic outcomes at 48 weeks are published; data collection for efficacy outcomes was ongoing at the time of FDA approval.

Patients enrolled in the trial had DMD with mutations amenable to exon 53 skipping, were on average 8 years of age, were on corticosteroids for a mean duration of 3 years (minimum 6 months), had a mean percent predicted forced expiratory volume (ppFVC) of 93%, and had stable lung and cardiac function which was not expected to decline.[1,7] Efficacy of different doses was not evaluated in Part 1, and there was no dose-response or correlation observed with number of doses or duration of exposure and dystrophin production.[1] The highest dose (30 mg/kg weekly) was used for the Part 2 extension study. After 48 weeks of treatment, the mean dystrophin protein was 1.02% of normal (SD 1.03%) compared to an average value of 0.095% (SD 0.068%) at baseline (mean increase of 0.9% of normal).[1] Seven patients (28%) had a dystrophin level which remained below the lower limit of quantification for Western blot analysis (0.25% of normal) at 48 weeks.[1,7] Twelve patients (48%) had a dystrophin level that was less than 0.5% of normal, and only 2 patients had a dystrophin level over 2%.[7] This is similar to the change in dystrophin observed with eteplirsen treatment over 48 weeks in patients with mutations amenable to exon 51 skipping.[9] There is no consensus on what may constitute a clinically important change in dystrophin protein, as dystrophin levels have yet to be correlated to clinically relevant outcomes, and it is not clear if the truncated protein produced is functional. Additionally, the lack of a placebo group in Part 2 of the study increases risk

of biases and limits interpretation of these results as there is no method to evaluate changes in function, symptoms, or quality of life compared to the natural disease progression.

While data collection for functional outcomes is ongoing, available data was evaluated by the FDA. Functional outcomes up to 96 weeks are available for 24 of the 25 patients. Current data indicates a progressive decline in the average change in 6MWT from baseline of 26.1m at 48 weeks (n=25), 52.2 m at 72 weeks (n=25), 64.6 m at 96 weeks (n=24) and 86.1 m at 120 weeks (n=21).[7] Because there was no control group in this study, comparisons to placebo or no treatment are difficult to make, but FDA reviewers noted that this trend does not appear to be substantially different than natural history data for DMD patients.[7] In addition, there was no positive correlation between the change in 6MWT per year and change in dystrophin level (R=0.14), indicating that increases in a truncated dystrophin protein may not be an adequate surrogate marker for functional improvement.[7] Slight numerical declines were also noted in the average ppFVC ranging from 0.6% at 48 weeks (n=25) to 3.7% at 120 weeks (n=21).[7] The average decline in ppFVC for 18 patients at 144 weeks was -5.3%; data collection for the remaining patients is ongoing.[7] It is unclear if these changes represent clinically significant differences for DMD patients as baseline ppFVC was high (mean 93%) and pulmonary symptoms are not typically present until FVC declines further.

Like eteplirsen, the clinical benefit of golodirsen for DMD has not yet been established. Currently available data indicate no change in disease progression and only slight increases in dystrophin. In addition, use of a single-arm, open-label study design limits interpretation and increases risk of bias, particularly for functional outcomes such as the 6MWT or NSAA where performance is susceptible to expectation bias and coaching which significantly confounds the benefit observed in an open-label trial when compared to a historical disease progression. Significant exclusion criteria limit applicability in severe or progressive disease as patients were only included if they had stable cardiac and pulmonary function that, in the investigator's opinion, were unlikely to decompensate over the duration of the study. Additional data are needed to confirm clinical benefit. A confirmatory, placebo-controlled efficacy study evaluating golodirsen in patients with DMD and mutations amenable to exon 53 skipping is ongoing with planned enrollment of approximately 222 patients.[7]

Clinical Safety:

Sixty patients with exposure to golodirsen from 2 ongoing studies were included in the safety analysis. Twenty-three patients were treated for more than 2 years, 23 were treated for more than 1 year and 11 were treated for less than 1 year.[7] Severe adverse events were infrequent and occurred in 2 patients with exposure to golodirsen (osteoporosis, fracture, and rhabdomyolysis) and in one patient randomized to placebo (fracture).[7] To date, none of the patients in ongoing trials have discontinued treatment due to adverse events.[7] While there were few serious adverse events documented in the study for golodirsen, the number of patients exposed to golodirsen is small and unlikely to detect rare adverse events. In the golodirsen clinical trial program and in safety reports at the time of FDA approval, there were no documented adverse events related to infection or renal problems. However, FDA reviewers noted risk for renal adverse events in pre-clinical animal studies and risk of infection associated with eteplirsen, a molecule with similar administration.[7]

In studies of rats, abnormalities in kidney function were observed including increases in blood urea nitrogen, creatinine, and included several instances of renal failure leading to death.[7] These adverse events were observed at doses which would result in plasma exposure of about 2.6 times higher than the FDA recommended dose.[7] Because golodirsen is primarily excreted unchanged in the urine, worsening renal function could lead to increased exposure and the potential for increased risk of renal adverse events.[7] Based on this information, FDA-labeling includes recommendations for renal monitoring. However, because patients with DMD typically have reduced muscle mass, serum creatinine levels are likely not an accurate measure of renal function for DMD patients.[7] Instead monitoring recommendations include baseline glomerular filtration rate via 24-hour urine collection, monthly assessments of proteinuria, and assessment of serum cystatin C every 3 months.[8] Reassessment of glomerular filtration rate is recommended if proteinuria or elevated serum cystatin C is observed.[8]

FDA reviewers also noted the potential for serious infection associated with indwelling IV ports, particularly in patients receiving chronic corticosteroids.[7] This concern was based on a review of post-marketing adverse event data for eteplirsen. Of the 469 patients known to be exposed to commercial eteplirsen, 11 cases (2.3%) of device infections, bacteremia, and sepsis had been reported through the FDA's Adverse Event Reporting System.[7] Because the FDA relies on voluntary reporting for clinicians, the exact incidence of these adverse events or occurrence for patients prescribed chronic corticosteroids is unknown. During clinical trials for golodirsen, there were no reports of serious infection. However, only half of patients treated with golodirsen (~30) received drug infusions via a central venous access port.[7]

Common adverse events are listed in **Table 1**. Of note, falls, fractures, accidents, and injuries were more common with treatment compared to placebo.[7] The exact etiology of these adverse events is unknown and confounding factors may include the degree of patient activity and DMD disease progression. In addition, hypersensitivity reactions requiring medical intervention were more common with golodirsen compared to placebo and labeling includes warnings for hypersensitivity reactions. The most common reactions included rash, pyrexia, pruritus, moderate urticaria, and dermatitis.[7]

Post-marketing requirements include studies to evaluate immune response to truncated dystrophin protein, carcinogenicity in animals, and a confirmatory trial evaluating clinical benefit.

Table 1. Adverse events occurring in more than 10% of patients and more common than placebo.[7]

Adverse Event	**Golodirsen (%) N=60**	**Placebo (%) N=21**
Headache	41	10
Pyrexia	41	14
Fall	29	19
Abdominal pain	27	10
Nasopharyngitis	27	14
Cough	27	19
Vomiting	27	19
Nausea	20	10
Administration site pain	17	0
Back pain	17	5
Pain	17	5
Dizziness	15	5
Ligament sprain	12	5

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Functional or symptom improvement (motor, pulmonary, or cardiovascular)
2) Quality of life
3) Disease progression

Primary Study Endpoints:

1) Biologic: Dystrophin protein levels at week 48
2) Efficacy: 6MWT at week 144

4) Serious adverse events
5) Study withdrawal due to an adverse event

Table 2. Pharmacology and Pharmacokinetic Properties.[8]

Parameter	
Mechanism of Action	Golodirsen 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
Distribution and Protein Binding	Volume of distribution of 668 mL/kg after 30 mg/kg dose Protein binding of 33-39%
Elimination	Excreted unchanged in the urine
Half-Life	3.4 hours (SD 0.6) with no apparent variation based on age or weight
Metabolism	N/A

Abbreviations: N/A = not applicable; SD = standard deviation

Table 3. 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. Frank, et al.[1] FDA Clinical Review[7] Phase I/II, DB, PC, RCT NCT02310906	Part 1: 1. Golodirsen IV 4-30 mg/kg weekly 2. Placebo 12 weeks In part 1, dose was initiated at 4 mg/kg for 2 weeks then patients were randomized to 10, 20 or 30 mg/kg doses followed by dose titration up to 30 mg/kg at 2 week intervals Part 2: Patients from part 1 were enrolled in a Part 2 open-label phase of golodirsen IV 30 mg/kg weekly for 144 weeks. Part 2 is ongoing and enrolled an additional 13 patients.	Demographics: Part 2: - Age 8.2 y (SD 2.2) - Median BMI 18.1 kg/m^2 - 6MWT 403.7m (SD 56.7) - Corticosteroid duration of therapy: 36.8 months (SD 25.9) - Mean ppFVC 92.7%[7] Key Inclusion Criteria: - 6-15 years of age - DMD diagnosis - Out-of-frame deletions amenable to exon 53 skipping - 6MWT ≥ 250 m - NSAA > 17 or Rise (Gowers) time < 7 seconds - LVEF ≥ 50% - QTc < 450 ms - ppFVC ≥ 50% - Stable oral corticosteroid for at least 24 weeks Key Exclusion Criteria: - Nocturnal ventilator support - Other treatment which may affect muscle strength or function - Planned major surgery - Change in contracture treatment within 3 months - Other clinically significant illness which would interfere with participation	ITT: Part 1: 1. 8 2. 4 Part 2: 25 Attrition: Part 1: 1. 0 2. 0 Part 2: 2 (8%)[7]	Primary Endpoint: Change from baseline in dystrophin protein level at Week 48 (Western blot analysis) Baseline: - Mean: 0.095% - SD: 0.068% - Range: 0.020-0.31% Week 48: - Mean: 1.019% - SD: 1.033% - Range: 0.09-4.30% MD 0.92% (SD 1.01)[7] 6MWT at 144 weeks: NR Secondary Endpoints: Pulmonary Function Tests: NR	NA for all	Moderate treatment emergent AE: 2 No serious AE or discontinuations due to AE were reported	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: HIGH. Part 1 randomized via IVRS, but baseline characteristics were unbalanced likely as a result of small sample size. Patients in golodirsen group were on average older, had longer time since diagnosis, and had longer duration of corticosteroid treatment. No randomization in Part 2. Performance Bias: HIGH. Part 1 double-blinded, but method of blinding for patients and providers was unspecified. 2 protocol violations regarding unblinding were noted.[7] Part 2 was open-label. Objective measures (e.g. dystrophin) are less likely to be affected by performance bias than functional measures (e.g., 6MWT). Detection Bias: LOW. Assessors of tissue analyses blinded to individual patients, time of biopsy, and treatment status via "blinding codes". Attrition Bias: LOW. All patients completed initial 12 weeks. To date, 2 patients have withdrawn from the ongoing part 2 analysis for reasons unrelated to treatment. Reporting Bias: LOW. Biologic outcomes reported as specified. Data on functional outcomes was not reported as part 2 of the study remains ongoing. Other Bias: HIGH. Funding provided by Sarepta pharmaceuticals who was involved in data collection, analysis, interpretation, and writing the manuscript. Multiple authors (including the primary author) were employees and may own stock in the company. **Applicability**: Patient: Included patients had stable cardiovascular disease, lung function ppFVC ≥50%, and baseline motor function tests which limits applicability to patients with more severe or progressive disease. Intervention: Dose appropriate for a phase I pharmacokinetic dose-finding trial. Efficacy of different doses was not evaluated. There was no correlation observed with number of doses or duration of exposure and dystrophin production. Comparator: Lack of control group after 12 weeks limits conclusions regarding efficacy of treatment or long-term safety. Placebo comparison would have been more useful. Outcomes: Functional outcomes not reported. Correlation of 6MWT or other functional outcomes with dystrophin levels is unclear. Setting: Centers in the United Kingdom, France, and Italy.

Abbreviations [alphabetical order]: 6MWT = 6 minute walk test; AE = adverse events; ARR = absolute risk reduction; CI = confidence interval; DB = double-blind; DMD = Duchenne muscular dystrophy; ITT = intention to treat; IV = intravenous; IVRS = interactive voice response system; LVEF = left ventricular ejection fraction; MD = mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NSAA = North Star Ambulatory Assessment; PC = placebo-controlled; PP = per protocol; ppFVC = percent predicted forced expiratory volume; RCT = randomized controlled trial; SD = standard deviation; y = years

References:

1. Frank DE, Schnell FJ, Akana C, et al. Increased dystrophin production with golodirsen in patients with Duchenne muscular dystrophy. *Neurology.* 2020:10.1212/WNL.0000000000009233.
2. Duchenne and Becker Muscular Dystrophies. In Dynamed. [internet database]. Ipswich, MA: EBSCO Publishing, Inc. Updated December 23, 2019. Accessed March 18, 2020.
3. Theadom A, Rodrigues M, Roxburgh R, et al. Prevalence of muscular dystrophies: a systematic literature review. *Neuroepidemiology.* 2014;43(3-4):259-268.
4. Gloss D, Moxley RT, 3rd, Ashwal S, Oskoui M. 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.
5. Golodirsen FDA Administrative and Correspondence Documents. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211970Orig1s000AdminCorres.pdf. Accessed May 5, 2020.
6. Exondys 51 Summary Review. US Food and Drug Administration Center for Drug Evaluation and Research. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_Redacted.pdf. Accessed February 2, 2017.
7. Golodirsen FDA Clinical review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211970Orig1s000MedR.pdf. Accessed March 11, 2020.
8. Vyondys 53 (golodirsen injection) [package insert] Cambridge, MA: Sarepta Therapeutics, Inc.; 2020.
9. Exondys 51 (eteplirsen injection) [package insert] Cambridge, MA: Sarepta Therapeutics, Inc.; 2018.
10. Kinane TB, Mayer OH, Duda PW, Lowes LP, Moody SL, Mendell JR. 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.
11. Khan N, Eliopoulos H, Han L, et al. Eteplirsen Treatment Attenuates Respiratory Decline in Ambulatory and Non-Ambulatory Patients with Duchenne Muscular Dystrophy. *Journal of neuromuscular diseases.* 2019;6(2):213-225.
12. Alfano LN, Charleston JS, Connolly AM, et al. Long-term treatment with eteplirsen in nonambulatory patients with Duchenne muscular dystrophy. *Medicine.* 2019;98(26):e15858.
13. Exondys 51 Medical Review. US Food and Drug Administration Center for Drug Evaluation and Research. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488Orig1s000MedR.pdf. Accessed February 2, 2017.
14. Wilton SD, Veedu RN, Fletcher S. The emperor's new dystrophin: finding sense in the noise. *Trends in Molecular Medicine.* 2015;21(7):417-426.
15. McDonald CM, Henricson EK, Abresch RT, et al. The 6-minute walk test and other clinical endpoints in duchenne muscular dystrophy: reliability, concurrent validity, and minimal clinically important differences from a multicenter study. *Muscle Nerve.* 2013;48(3):357-368.
16. Geiger R, Strasak A, Treml B, et al. Six-Minute Walk Test in Children and Adolescents. *The Journal of Pediatrics.* 2007;150(4):395-399.e392.
17. Ulrich S, Hildenbrand FF, Treder U, et al. Reference values for the 6-minute walk test in healthy children and adolescents in Switzerland. *BMC Pulmonary Medicine.* 2013;13(1):49.

18. Mendell JR, Goemans N, Lowes LP, et al. Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy. *Annals of neurology.* 2016;79(2):257-271.
19. Mazzone E, Martinelli D, Berardinelli A, et al. North Star Ambulatory Assessment, 6-minute walk test and timed items in ambulant boys with Duchenne muscular dystrophy. *Neuromuscular disorders : NMD.* 2010;20(11):712-716.

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
prednisone	PREDNISONE INTENSOL	ORAL CONC	PO
prednisone	PREDNISONE	SOLUTION	PO
prednisone	PREDNISONE	TAB DS PK	PO
prednisone	PREDNISONE	TABLET	PO
prednisone	RAYOS	TABLET DR	PO

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to March 09, 2020

1	eteplirsen.mp.	116
2	golodirsen.mp.	15
3	exp Glucocorticoids/	190109
4	deflazacort.mp.	569
5	Muscular Dystrophy, Duchenne/	5280
6	1 or 2 or 3 or 4	190528
7	5 and 6	318
8	limit 7 to (english language and humans)	266
9	limit 8 to yr="2019 -Current"	16

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VYONDYS 53™ safely and effectively. See full prescribing information for VYONDYS 53.

VYONDYS 53 (golodirsen) injection, for intravenous use
Initial U.S. Approval: 2019

INDICATIONS AND USAGE

VYONDYS 53 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 VYONDYS 53. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials. (1)

DOSAGE AND ADMINISTRATION

- Measure glomerular filtration rate prior to initiation (2.1)
- 30 milligrams per kilogram once weekly (2.2)
- Administer as an intravenous infusion over 35 to 60 minutes (2.2, 2.4)
- Dilution required prior to administration (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/2 mL (50 mg/mL) in a single-dose vial (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions: Hypersensitivity reactions, including rash, pyrexia, pruritus, urticaria, dermatitis, and skin exfoliation have occurred in patients who were treated with VYONDYS 53. If a hypersensitivity reaction occurs, institute appropriate medical treatment and consider slowing the infusion or interrupting the VYONDYS 53 therapy. (2.3, 5.1)
- Renal Toxicity: Based on animal data, may cause renal toxicity. Renal function should be monitored; creatinine may not be a reliable measure of renal function in DMD patients. (5.2, 13.2)

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥20% and higher than placebo) were headache, pyrexia, fall, abdominal pain, nasopharyngitis, cough, vomiting, and nausea. (6.1)

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

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2019

Appendix 4: Key Inclusion Criteria

Population	Duchenne Muscular Dystrophy
Intervention	Drugs in Appendix 1
Comparator	Drugs in Appendix 1
Outcomes	Symptoms (e.g., muscle, pulmonary, cardiac, etc), quality of life, functional improvement, disease progression, morbidity, or mortality
Setting	Outpatients

Appendix 5: Prior Authorization Criteria

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

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the drug being used to treat an OHP-funded condition?	**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, golodirsen, and deflazacort are not indicated for other forms of muscular dystrophy or other diagnoses.
4. Is the request for continuation of treatment?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5
5. Is the request for deflazacort?	**Yes:** Go to #6	**No:** Go to #9
6. Is the patient ≥ 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, and at least 2 doses of 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?	**Yes:** Approve for up to 12 months. Document contraindication or intolerance reaction.	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of prednisone.
9. Is the request for an FDA-approved indication (Table 1)?	**Yes:** Go to #10 Document genetic testing.	**No:** Pass to RPh, Deny; medical appropriateness.
10. Is the request for golodirsen?	**Yes:** Go to #11	**No:** Go to #12
11. Has the provider documented glomerular filtration rate as evaluated by a 24 hour urine collection 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 or 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?	**Yes:** Go to #2	**No:** Go to #3

Renewal Criteria		
2. Has the provider assessed renal function? Recommended monitoring includes proteinuria monthly and serum cystatin C every three months. If results are abnormal, a 24H urine collection should be performed.	**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: *6/20 (SS); 09/19; 11/17; 07/17 (SS)*
Implementation: *7/1/20; 11/1/19; 1/1/18; 9/1/17*