

**EFFECTIVE DATE:** 11 | 01 | 2022

**POLICY LAST UPDATED:** 07 | 20 | 2022

## OVERVIEW

Duchenne muscular dystrophy is an inherited disorder that results in progressive muscle weakness and loss of muscle mass, primarily affecting males. Duchenne muscular dystrophy results from non-sense or frame-shifting variant(s) in the Duchenne muscular dystrophy gene which is responsible for producing dystrophin, a cohesive protein essential for maintaining muscle support and strength. Antisense oligonucleotides are short, synthetic, single-stranded oligodeoxynucleotides that selectively bind to specific exons of the dystrophin pre-messenger RNA causing the exon to be skipped and thereby repairing the mutated reading frame resulting in production of an internally truncated, yet functional, dystrophin protein. Four antisense oligonucleotides—eteplirsen, golodirsen, viltolarsen, and casimersen have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of Duchenne muscular dystrophy. Each targets a specific exon. For example, eteplirsen targets skipping of exon 51, golodirsen and viltolarsen target skipping of exon 53, and casimersen targets skipping of exon 45.

## MEDICAL CRITERIA

Not applicable.

## PRIOR AUTHORIZATION

Not applicable.

## POLICY STATEMENT

### Medicare Advantage Plans

The use of antisense oligonucleotides (such as eteplirsen, golodirsen, viltolarsen, and casimersen) are not covered for all indications including treatment of Duchenne muscular dystrophy as the evidence is insufficient to determine the effects of the technology on health outcomes.

### Commercial Products

The use of antisense oligonucleotides (such as eteplirsen, golodirsen, viltolarsen, and casimersen) are not medically necessary for all indications including treatment of Duchenne muscular dystrophy as the evidence is insufficient to determine the effects of the technology on health outcomes.

## COVERAGE

Benefits may vary between groups/contracts. Please refer to the appropriate Evidence of Coverage for applicable physician administered drug infusion coverage/benefits.

## BACKGROUND

Duchenne muscular dystrophy is an X-linked, recessive disorder that occurs in approximately 1 in every 3500 to 5000 males. It primarily affects males. However, a small number of females are also affected, but they are usually asymptomatic, and even when symptomatic, only present with a mild form of the disease. According to U.S. epidemiologic data, the first signs or symptoms of Duchenne muscular dystrophy are noted at a mean age of 2.5 years (range, 0.2-1 years), and the mean age at definitive diagnosis is 4.9 years (range, 0.3-8.8 years). Symptoms include motor difficulties such as running, jumping, walking up stairs, and an unusual waddling gait. Some improvement in symptoms may be seen from 3 to 6 years of age, though gradual deterioration resumes and most patients lose ambulation by age 12 and require noninvasive ventilation by late teenage

years. Patients progress from needing noninvasive ventilation only during night sleeping, followed by noninvasive ventilation during day and night sleeping, and then noninvasive ventilation during day and night over the course of 5 to 10 years.

Duchenne muscular dystrophy occurs as a result of variant(s) in the gene responsible for producing dystrophin, a cohesive protein that is essential for maintaining muscle support and strength. Duchenne muscular dystrophy is the longest known human gene, and several variants can cause Duchenne muscular dystrophy. Most deletion variants disrupt the translational reading frame in the dystrophin messenger RNA resulting in an unstable, nonfunctional dystrophin molecule. As a result, there is progressive muscle degeneration leading to loss of independent ambulation, as well as other complications, including respiratory and cardiac complications. Genetic testing is required to determine the specific Duchenne muscular dystrophy gene variant(s) for a definitive diagnosis, even when the absence of dystrophin protein expression has been confirmed by muscle biopsy. There are over 4700 variants in the Leiden Duchenne muscular dystrophy mutation database, and the most common variants are concentrated between exons 45 and 53.

The current standard of pharmacotherapy for Duchenne muscular dystrophy is corticosteroids for all patients regardless of genetic variant. Treatment is initiated once patients reach a plateau of motor skill development, generally at ages 4 to 6 years, but prior to onset of motor decline. The goal of corticosteroid therapy is to preserve ambulation and minimize respiratory, cardiac, and orthopedic complications. In addition, muscle weakness and pain, cardiac, pulmonary, orthopedic, and endocrine symptoms should be managed.

## **Regulatory Status**

### **Eteplirsen**

In September 2016, eteplirsen (Exondys 51™; Sarepta Therapeutics) was approved by the U.S. Food and Drug Administration (FDA) after orphan drug designation for Duchenne muscular dystrophy patients who have a confirmed variant of the Duchenne muscular dystrophy gene that is amenable to exon 51 skipping. This indication was approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with eteplirsen.

The FDA, under the accelerated approval regulations (21 CFR 314.510), requires that Sarepta conduct a confirmatory trial to demonstrate the clinical benefit of eteplirsen. In the preceding 3 years after the FDA approval, there has still been no publication of a trial confirming or refuting a clinical benefit of eteplirsen. The European Medicines Agency rejected marketing approval for eteplirsen in September 2018.

For individuals with a confirmed variant of the Duchenne muscular dystrophy gene that is amenable to exon 51 skipping who receive eteplirsen, the evidence includes 1 randomized controlled trial (RCT), 1 ongoing prospective open-label trial with a concurrent untreated control arm and multiple post-hoc studies with historical control. Relevant outcomes are disease-specific survival, change in disease status, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. For the single pivotal RCT, no formal sample size calculations were conducted. A sample size of 12 total participants was selected with 4 participants in 3 treatment groups. There was no statistically significant difference either in the mean change from baseline in the 6-minute walk test distance or change in the North Star Ambulatory Assessment total score between eteplirsen-treated participants and placebo-treated patients at week 48. While eteplirsen treatment resulted in dystrophin detection in muscle biopsies suggesting the production of (truncated) dystrophin, the amount of protein produced was very limited according to the Western blot results (0.44% of normal dystrophin at week 48 [Study 301]; 0.93% at week 180 [Study 201/202]). There are no satisfactory data, clearly establishing the effectiveness of the truncated dystrophin. Further, the minimum beneficial amount of dystrophin expression to be translated into a clinical benefit has yet to be established. In the absence of clinical data convincingly demonstrating a clinical effect, it cannot be concluded that the amount of dystrophin expressed with eteplirsen will translate into a clinical benefit to patients. Multiple analysis of long-term follow-up data from study 201/202 and 301 on functional outcome measures such as 6-minute walk test and pulmonary function suggest that the rate of decline in eteplirsen-treated participants was

less as compared to historical controls. However, the post-hoc nature of the analysis and the fact that the cohorts were retrospectively identified within the untreated group of patients is of serious concern (potential selection bias) and undermines the robustness of the data. Particularly, the 6-minute walk test is subject to inter- and intra-subject variability and is influenced by training and motivation making it a less suitable outcome measure for external control group comparison. Thus the clinical benefit of treating Duchenne muscular dystrophy with eteplirsen, including improved motor function and pulmonary function, has not been demonstrated. A confirmatory, prospective and adequately powered trial is necessary to assess the net health benefit of eteplirsen in patients with Duchenne muscular dystrophy amenable to 51 skipping. The evidence is insufficient to determine the effects of the technology on health outcomes.

### **Golodirsen**

In December 2019, golodirsen (Vyondys 53™; Sarepta Therapeutics) was approved by the FDA for treatment of Duchenne muscular dystrophy patients who have a confirmed variant of the Duchenne muscular dystrophy gene that is amenable to exon 53 skipping. This indication was approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with golodirsen.

The FDA, under the accelerated approval regulations (21 CFR 314.510), requires that Sarepta conduct a randomized double-blind, placebo-controlled trial of 96 weeks with an open-label extension to 144 weeks to verify the clinical benefit of golodirsen with the primary endpoint of 6-minute walk test. The expected date of trial completion is April 2024 and final report submission to the FDA by October 2024.

For individuals with a confirmed variant of the Duchenne muscular dystrophy gene that is amenable to exon 53 skipping who receive golodirsen, the evidence includes a 1-part multicenter study which consists of a part 1 randomized, double-blind safety and tolerability study and a part 2 open-label efficacy and safety study. Results of interim analysis were based on 25 participants who received a weekly intravenous infusion of golodirsen 30 mg/kg. At week 48, the mean change in dystrophin protein levels was 0.924% increase from the baseline (1.019% vs. 0.095%;  $P < 0.001$ ). There are no satisfactory data, clearly establishing the effectiveness of the truncated dystrophin. Further, the minimum beneficial amount of dystrophin expression to be translated into a clinical benefit has yet to be established. In the absence of clinical data convincingly demonstrating a clinical effect, it cannot be concluded that the amount of dystrophin expressed with golodirsen will translate into a clinical benefit to patients. A confirmatory, prospective and adequately powered trial is necessary to assess the net health benefit of eteplirsen in patients with Duchenne muscular dystrophy amenable to 53 skipping. The evidence is insufficient to determine the effects of the technology on health outcomes.

### **Viltolarsen**

In August 2020, viltolarsen (Viltepso™; Nippon Shinyaku Co.) was approved by the FDA for the treatment of Duchenne muscular dystrophy patients who have a confirmed mutation of the Duchenne muscular dystrophy gene that is amenable to exon 53 skipping. This indication was approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in participants treated with viltolarsen.

The FDA, under the accelerated approval regulations (21 CFR 314.510), requires that Nippon Shinyaku Co. conduct a randomized, double-blind, placebo-controlled trial over 48 weeks to verify the clinical benefit of viltolarsen with the primary endpoint "time to stand". The expected date of trial completion is July 2024 and final report submission to the FDA by December 2024.

For individuals with a confirmed variant of the Duchenne muscular dystrophy gene that is amenable to exon 53 skipping who receive viltolarsen, the evidence includes a 2-part multicenter study which consists of a part 1 randomized, double-blind safety and tolerability study and a part 2 open-label efficacy and safety study. Relevant outcomes are disease-specific survival, change in disease status, functional outcomes, health status

measures, quality of life, and treatment-related mortality and morbidity. In 8 participants who received a weekly intravenous infusion of viltolarsen 80 mg/kg, the mean increase in dystrophin protein levels from baseline was 5.3% ( $\pm 4.5$ ) of normal levels ( $p=.01$ ) at week 25. There are no satisfactory data clearly establishing the effectiveness of the truncated dystrophin. Further, the minimum beneficial amount of dystrophin expression to be translated into a clinical benefit has yet to be established. Outcomes derived from several timed function and muscle strength tests improved among participants treated with viltolarsen compared to a matched natural history control group. However, given the variability in the natural history of Duchenne muscular dystrophy, comparison to a natural history cohort has limited reliability. Further, the clinical relevance of the observed differences is unknown. In the absence of clinical data convincingly demonstrating a clinical effect, it cannot be concluded that the amount of dystrophin expressed with viltolarsen will translate into a clinical benefit to patients. A confirmatory, prospective and adequately powered trial is necessary to assess the net health benefit of viltolarsen in patients with Duchenne muscular dystrophy amenable to 53 skipping. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

### **Casimersen**

In February 2021, casimersen (Amondys45™; Sarepta Therapeutics) was approved by the FDA for the treatment of Duchenne muscular dystrophy patients who have a confirmed mutation of the Duchenne muscular dystrophy gene that is amenable to exon 45 skipping. This indication was approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in participants treated with casimersen.

The FDA, under the accelerated approval regulations (21 CFR 314.510), requires that Sarepta verify the clinical benefit of casimersen by completing Study 4045-301 (Essence), A Double-Blind, Placebo-Controlled, Multicenter Study with an Open-Label Extension to Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in participants with Duchenne Muscular Dystrophy. The study includes a randomized, double-blind, placebo-controlled period of 96 weeks and concludes after an open label extension period to 144 weeks. The primary endpoint will be the 6-minute walk test. The expected date of trial completion is April 2024 and final report submission to the FDA by October 2024.

For individuals with a confirmed variant of the Duchenne muscular dystrophy gene that is amenable to exon 45 skipping who receive casimersen, the evidence includes a single double-blind, placebo-controlled phase 3 trial. An interim analysis conducted at week 48 with data for 46 participants with exon 45 skipping (casimersen=27 and placebo=16) is available. Compared to those who received placebo, participants who received casimersen demonstrated a statistically significant increase in dystrophin production by 0.59% at week 48 as measured by Western blot. The mean change from baseline to week 48 in dystrophin production was 0.81% versus 0.22% ( $p=.004$ ) in the casimersen versus placebo arms, respectively. There are no satisfactory data clearly establishing the effectiveness of the truncated dystrophin. Further, the minimum beneficial amount of dystrophin expression to be translated into a clinical benefit has yet to be established. In the absence of clinical data convincingly demonstrating a clinical effect, it cannot be concluded that the amount of dystrophin expressed with casimersen will translate into a clinical benefit to patients. A confirmatory, prospective and adequately powered trial is necessary to assess the net health benefit of casimersen in patients with Duchenne muscular dystrophy amenable to 45 skipping. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

### **CODING**

#### **Medicare Advantage Plans**

The following HCPCS codes are not covered:

- J1426** Injection, casimersen, 10 mg
- J1427** Injection, viltolarsen, 10 mg
- J1428** Injection, eteplirsen, 10 mg
- J1429** Injection, golodirsen, 10 mg

## Commercial Products

The following HCPCS codes are not medically necessary:

- J1426** Injection, casimersen, 10 mg
- J1427** Injection, viltolarsen, 10 mg
- J1428** Injection, eteplirsen, 10 mg
- J1429** Injection, golodirsen, 10 mg

## RELATED POLICIES

Not applicable.

## PUBLISHED

- Provider Update, September 2022
- Provider Update, September 2021
- Provider Update, October 2020
- Provider Update, July 2019
- Provider Update, June 2018

## REFERENCES

1. Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care. *Lancet Neurol.* Feb 2010; 9(2): 177-89. PMID 19945914
2. Center for Disease Control and Prevention. Muscular Dystrophy: MD STARnet Data and Statistics. 2016; <http://www.cdc.gov/ncbddd/musculardystrophy/data.html>. Accessed March 20, 2022.
3. Falzarano MS, Scotton C, Passarelli C, et al. Duchenne Muscular Dystrophy: From Diagnosis to Therapy. *Molecules.* Oct 07 2015; 20(10): 18168-84. PMID 26457695
4. Committee for Medicinal Products for Human Use (CHMP) Assessment Report: Exondys. Published September 20, 2018, Available at [https://www.ema.europa.eu/en/documents/assessment-report/exondys-epar-refusal-public-assessment-report\\_en.pdf](https://www.ema.europa.eu/en/documents/assessment-report/exondys-epar-refusal-public-assessment-report_en.pdf). Accessed March 20, 2022.
5. Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment Guidance for Industry. Published February 2018. <https://www.fda.gov/media/92233/download>. Accessed March 21, 2022.
6. McDonald CM, Henricson EK, Abresch RT, et al. The 6-minute walk test and other endpoints in Duchenne muscular dystrophy: longitudinal natural history observations over 48 weeks from a multicenter study. *Muscle Nerve.* Sep 2013; 48(3): 343-56. PMID 23681930
7. Henricson E, Abresch R, Han JJ, et al. The 6-Minute Walk Test and Person-Reported Outcomes in Boys with Duchenne Muscular Dystrophy and Typically Developing Controls: Longitudinal Comparisons and Clinically-Meaningful Changes Over One Year. *PLoS Curr.* Jul 08 2013; 5. PMID 23867975
8. Mendell JR, Rodino-Klapac LR, Sahenk Z, et al. Eteplirsen for the treatment of Duchenne muscular dystrophy. *Ann Neurol.* Nov 2013; 74(5): 637-47. PMID 23907995
9. Mendell JR, Goemans N, Lowes LP, et al. Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy. *Ann Neurol.* Feb 2016; 79(2): 257-71. PMID 26573217
10. McDonald CM, Shieh PB, Abdel-Hamid HZ, et al. Open-Label Evaluation of Eteplirsen in Patients with Duchenne Muscular Dystrophy Amenable to Exon 51 Skipping: PROMOVI Trial. *J Neuromuscul Dis.* 2021; 8(6): 989-1001. PMID 34120909
11. Food and Drug Administration. FDA Briefing Document: Peripheral and Central Nervous System Drugs Advisory Committee Meeting, April 25, 2016. NDA 206488.Eteplirsen. 2016; <https://www.fda.gov/media/97306/download>. Accessed March 22, 2022.
12. Woodcock J, Dunn B. FDA Presentations for the April 25, 2016 Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee. 2016; <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM500821.pdf>. Accessed March 20, 2022.
13. Center for Drug Evaluation and Research. Application Number: 206488orig1s000. Summary Review. 2016; [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2016/206488\\_summary%20review\\_Redacted.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_Redacted.pdf). Accessed March 19, 2022.

14. Kesselheim AS, Avorn J. Approving a Problematic Muscular Dystrophy Drug: Implications for FDA Policy. *JAMA*. Dec 13 2016; 316(22): 2357-2358. PMID 27775756
15. Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy: Effectiveness and Value. Institute for Clinical and Economic Review. [https://icer-review.org/wp-content/uploads/2018/12/ICER\\_DMD-Final-Report\\_081519-1.pdf](https://icer-review.org/wp-content/uploads/2018/12/ICER_DMD-Final-Report_081519-1.pdf). Accessed March 21, 2022.
16. Khan N, Eliopoulos H, Han L, et al. Eteplirsen Treatment Attenuates Respiratory Decline in Ambulatory and Non-Ambulatory Patients with Duchenne Muscular Dystrophy. *J Neuromuscul Dis*. 2019; 6(2): 213-225. PMID 30856119
17. 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*. Feb 03 2018; 391(10119): 451-461. PMID 29174484
18. Kinane TB, Mayer OH, Duda PW, et al. Long-Term Pulmonary Function in Duchenne Muscular Dystrophy: Comparison of Eteplirsen-Treated Patients to Natural History. *J Neuromuscul Dis*. NA 2018; 5(1): 47-58. PMID 29278896
19. Alfano LN, Charleston JS, Connolly AM, et al. Long-term treatment with eteplirsen in nonambulatory patients with Duchenne muscular dystrophy. *Medicine (Baltimore)*. Jun 2019; 98(26): e15858. PMID 31261494
20. Mitelman O, Abdel-Hamid HZ, Byrne BJ, et al. A Combined Prospective and Retrospective Comparison of Long-Term Functional Outcomes Suggests Delayed Loss of Ambulation and Pulmonary Decline with Long-Term Eteplirsen Treatment. *J Neuromuscul Dis*. 2022; 9(1): 39-52. PMID 34420980
21. Prescribing Label: VYONDYS 53 (golodirsen) injection, for intravenous use. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/211970s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211970s000lbl.pdf). Accessed March 21, 2022.
22. Frank DE, Schnell FJ, Akana C, et al. Increased dystrophin production with golodirsen in patients with Duchenne muscular dystrophy. *Neurology*. May 26 2020; 94(21):e2270-e2282. PMID 32139505
23. Clemens PR, Rao VK, Connolly AM, et al. Safety, Tolerability, and Efficacy of Viltolarsen in Boys With Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping: A Phase 2 Randomized Clinical Trial. *JAMA Neurol*. Aug 01 2020; 77(8): 982-991. PMID 32453377
24. Center for Drug Evaluation and Research. Application Number: 212154Orig1s000. Summary Review. Available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2020/212154Orig1s000SumR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/212154Orig1s000SumR.pdf). Accessed on March 22, 2022.
25. Komaki H, Takeshima Y, Matsumura T, et al. Viltolarsen in Japanese Duchenne muscular dystrophy patients: A phase 1/2 study. *Ann Clin Transl Neurol*. Dec 2020;7(12): 2393-2408. PMID 33285037
26. Prescribing label VILTEPSO (viltolarsen) injection, for intravenous use. Initial U.S. Approval: 2020. Available at <https://www.vilteps.com/prescribing-information>. Accessed March 22, 2022
27. Wagner KR, Kuntz NL, Koenig E, et al. Safety, tolerability, and pharmacokinetics of casimersen in patients with Duchenne muscular dystrophy amenable to exon 45 skipping: A randomized, double-blind, placebo-controlled, dose-titration trial. *Muscle Nerve*. Sep 2021; 64(3): 285-292. PMID 34105177
28. Prescribing Label: Amondys 45 (casimersen) injection, for intravenous use. Available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2021/213026lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213026lbl.pdf). Accessed on March 21, 2022
29. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. *Lancet Neurol*. Apr 2018; 17(4): 347-361. PMID 29395990
30. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. *Lancet Neurol*. Mar 2018; 17(3): 251-267. PMID 29395989
31. Feingold B, Mahle WT, Auerbach S, et al. Management of Cardiac Involvement Associated With Neuromuscular Diseases: A Scientific Statement From the American Heart Association. *Circulation*. Sep 26 2017; 136(13): e200-e231. PMID 28838934
32. Gloss D, Moxley RT, 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*. Feb 02 2016; 86(5): 465-72. PMID 26833937

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