MEDICAL POLICY

POLICY TITLE	TREATMENT FOR DUCHENNE MUSCULAR DYSTROPHY
POLICY NUMBER	MP 2.382

Effective Date:	8/1/2023

POLICY | PRODUCT VARIATIONS | DESCRIPTION BACKGROUND
RATIONALE | DEFINITIONS | BENEFIT VARIATIONS
DISCLAIMER | CODING INFORMATION | REFERENCES
POLICY HISTORY

I. POLICY

The use of antisense oligonucleotides (such as eteplirsen, golodirsen, viltolarsen, and casimersen) are considered **investigational** for all indications including treatment of Duchenne muscular dystrophy. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with these medications.

Policy Guidelines

The recommended dose of eteplirsen is 30 mg/kg of body weight administered once weekly as a 35- to 60-minute intravenous infusion. Eteplirsen is supplied in single-dose vials containing 100 mg (50 mg/mL).

The recommended dose of Golodirsen is 30 mg/kg of body weight administered once weekly as a 35- to 60-minute intravenous infusion. Golodirsen is supplied in single-dose vials containing 100 mg (50 mg/mL).

The recommended dose of Viltolarsen is 80 mg/kg of body weight administered once weekly as a 60-minute intravenous infusion. Viltolarsen is supplied in single-dose vials containing 250 mg (50 mg/mL).

The recommended dose of casimersen is 30 mg/kg of body weight administered once weekly as a 35- to 60-minute intravenous infusion. Casimersen is supplied in single-dose vials containing 100 mg (50 mg/mL).

Cross-reference:

MP 2.257 – Genetic Testing for Duchenne and Becker Muscular Dystrophy

II. PRODUCT VARIATIONS

TOP

This policy is only applicable to certain programs and products administered by Capital Blue Cross please see additional information below, and subject to benefit variations as discussed in Section VI below.

POLICY TITLE	TREATMENT FOR DUCHENNE MUSCULAR DYSTROPHY
POLICY NUMBER	MP 2.382

FEP PPO:

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:

https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies .

III. DESCRIPTION/BACKGROUND

TOP

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 girls 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 upstairs, 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 the 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.

Regulatory Status

Eteplirsen

In September 2016, eteplirsen (Exondys 51™; Sarepta Therapeutics) was approved by the U.S. Food and Drug Administration (FDA) for treatment of Duchenne muscular dystrophy patients who have a confirmed variant of the *Duchenne muscular dystrophy* gene that is amenable to exon fifty-one 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.[4,]

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 fifty-three 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 a 6-minute walk test. The expected date of trial completion is April 2024 and final report submission to the FDA by October 2024.

Viltolarsen

In August 2020, Viltolarsen (Viltepso™) 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 fifty-three skipping. This indication was approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients 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 Dec 2024.

Casimersen

In February 2021, casimersen (Amondys45™) 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 forty-five skipping. This indication was approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients 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 Patients 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.

IV. RATIONALE

TOP

Summary of Evidence

Eteplirsen

For individuals with a confirmed variant of the *Duchenne muscular dystrophy* gene that is amenable to exon fifty-one skipping who receive eteplirsen, the evidence includes one randomized controlled trial (RCT), one ongoing prospective open-label trial with a concurrent untreated control arm, and multiple post-hoc studies with historical controls. 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 twelve total patients was selected with four patients in three 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 patients and placebo-treated patients at week forty-eight. 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 analyses 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 patients was less as compared to historical controls. However, the post-hoc nature of the analyses and the fact that the cohorts were retrospectively identified within the untreated group of patients is of serious concern due to 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 that the technology results in an improvement in the net health outcome.

Golodirsen

For individuals with a confirmed variant of the *Duchenne muscular dystrophy* gene that is amenable to exon fifty-three skipping who receive Golodirsen, 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. Results of an interim analysis were based on twenty-five patients who received a weekly intravenous infusion of Golodirsen 30 mg/kg. At

week 48, the mean change in dystrophin protein levels was a 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 that the technology results in an improvement in the net health outcome.

Viltolarsen

For individuals with a confirmed variant of the *Duchenne muscular dystrophy* gene that is amenable to exon fifty-three 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 patients who received a weekly intravenous infusion of Viltolarsen 80 mg/kg, the mean increase in dystrophin protein levels from baseline was 5.3% (±4.5) of normal levels (p=0.01) 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 patients 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

For individuals with a confirmed variant of the *Duchenne muscular dystrophy* gene that is amenable to exon forty-five 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 patients 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 forty-eight as measured by Western blot. The mean change from baseline to week 48 in dystrophin production was 0.81% versus 0.22% (p=0.004) 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.

Practice Guidelines and Position Statements

Centers for Disease Control and Prevention

In 2010, the U.S. Centers for Disease Control and Prevention convened a Duchenne muscular dystrophy Care Considerations Working Group. In 2010, the Working Group developed care recommendations and updated them in 2018. Their recommendations focus on the overall perspective on care, pharmacologic treatment, psychosocial management, rehabilitation, orthopedic, respiratory, cardiovascular, gastroenterology and nutrition, and pain issues, as well as general surgical and emergency room precautions. The Centers for Disease Control and Prevention recommended the use of corticosteroids to slow the decline in muscle strength and function in Duchenne muscular dystrophy. The Working Group did not make recommendations on the use of eteplirsen. However, eteplirsen is discussed briefly under the section on "Emerging treatments." In 2016, the Working Group stated that eteplirsen was approved by the U.S. Food and Drug Administration (FDA) for males with the dystrophin gene variant amenable to exon fifty-one skipping, which is about 13% of the males with Duchenne muscular dystrophy.

American Heart Association

In 2017, a statement from the American Heart Association addressed the treatment of cardiac issues in individuals with any of several neuromuscular diseases, including Duchenne muscular dystrophy. For patients with Duchenne muscular dystrophy, the Association recommended the use of glucocorticoids, among other medications. The statement does not address the use of eteplirsen. One of the statement's co-authors disclosed being an industry-supported investigator for the drug.

American Academy of Neurology

In 2016, the American Academy of Neurology published an updated practice guideline on the use of corticosteroids for the treatment of Duchenne muscular dystrophy. The Academy does not discuss the use of eteplirsen for Duchenne muscular dystrophy.

Institute for Clinical and Economic Review

The Institute for Clinical and Economic Review is assessing the comparative clinical effectiveness and value of Golodirsen for Duchenne muscular dystrophy. The Report concludes, "Data on patient-important outcomes with eteplirsen are extremely limited, and studies of dystrophin levels show increases that are of uncertain clinical/biologic importance. There is no high- or moderate-quality evidence demonstrating improvements in function with eteplirsen, as the available long-term data showing potential clinical benefits are observational with matched or historical controls and need to be confirmed in larger, ongoing trials. Furthermore, the main

outcome reported, 6-minute walk test, is subject to patient effort, which may lead to less precision in the outcome measure and affect the results of a small, unblinded study. There are no particularly concerning safety signals with eteplirsen but given the small number of patients and short follow-up times, harms could be missed. We consider the evidence to be insufficient ("I"), as certainty of net benefit based on currently available evidence is low."

V. BENEFIT VARIATIONS

TOP

The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits, and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VI. DISCLAIMER

TOP

Capital Blue Cross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VII. CODING INFORMATION

TOP

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement. The codes need to be in numerical order.

Investigational, therefore not covered:

Procedure Codes							
96365	J1426	J1427	J1428	J1429			

ICD-10-CM Diagnosis Code	Description
G71.00	Muscular dystrophy
G71.01	Duchenne or Becker muscular dystrophy
Z92.86	Personal history of gene therapy

VIII. REFERENCES

TOP

1. *Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol. Jan 2010; 9(1): 77-93. PMID 19945913*
2. *Center for Disease Control and Prevention. Muscular Dystrophy: MD STARnet Data and Statistics. 2016*
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.*
5. *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*
6. *Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment Guidance for Industry. Published February 2018.*
7. *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*
8. *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*
9. *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*
10. *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*
11. *Food and Drug Administration. FDA Briefing Document: Peripheral and Central Nervous System Drugs Advisory Committee Meeting, April 25, 2016. NDA 206488. Eteplirsen. 2016*
12. *Woodcock J, Dunn B. FDA Presentations for the April 25, 2016, Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee. 2016*

13. *Center for Drug Evaluation and Research. Application Number: 206488orig1s000. Summary Review. 2016*
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. Updated April 22, 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. *Prescribing Label: VYONDYS 53 (golodirsen) injection, for intravenous use.*
21. *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*
22. *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*
23. *Center for Drug Evaluation and Research. Application Number: 212154Orig1s000. Summary Review.*
24. *Prescribing label VILTEPSO (viltolarsen) injection, for intravenous use. Initial U.S. Approval: 2020.*
25. *Prescribing Label: Amondys 45 (casimersen) injection, for intravenous use.*
26. *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*
27. *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*
28. *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*

29. 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

30. Blue Cross Blue Shield Association Medical Policy Reference Manual. 5.01.27, Treatment for Duchenne Muscular Dystrophy. June 2022.

IX. POLICY HISTORY

TOP

MP 2.382	**7/6/2022 New policy. BCBSA Full adoption.** Previously managed with Prime policies. FEP variation added. Codes applied.
	5/3/2023 Consensus review. References updated.

Top