

Corporate Medical Policy

Antisense Oligonucleotide Therapy for Duchenne Muscular Dystrophy

File Name: antisense_oligonucleotide_therapy_for_duchenne_muscular_dystrophy
Origination: 2/2017
Last CAP Review: 1/2021
Next CAP Review: 1/2022
Last Review: 3/2021

Description of Procedure or Service

Duchenne muscular dystrophy (DMD) 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 DMD 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 (NIV) by late teenage years. Patients progress from needing NIV only during night sleeping, followed by NIV during day and night sleeping, and then NIV during day and night over the course of five to ten years. DMD 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. *DMD* is the longest known human gene and several variants can cause DMD. Most deletion variants disrupt the translational reading frame in the dystrophin messenger RNA (mRNA) 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 *DMD* 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 DMD mutation database and the most common variants are concentrated between exons 45 and 53.

Eteplirsen is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) class. PMOs are stable oligonucleotide analogues that selectively bind to RNA to alter gene expression. In the case of eteplirsen, the PMO binds to exon 51 of the dystrophin premessenger RNA (pre-mRNA) causing the exon to be skipped and prevents that part of the code from being read during mRNA processing, thereby partially repairing the mutated reading frame in the mRNA coding sequence. As a result, eteplirsen enables the production of an internally truncated, yet functional, dystrophin protein.

Golodirsen is an antisense oligonucleotide of the PMO subclass. It binds to exon 53 of dystrophin pre-mRNA resulting in the exclusion of this exon during mRNA processing in patients with genetic variants that are amenable to exon 53 skipping. As a result, golodirsen, via exon 53 skipping, is intended to enable the production of an internally truncated dystrophin protein in patients with genetic variants amenable to exon 53 skipping.

Viltolarsen is an antisense oligonucleotide of the PMO subclass. It binds to exon 53 of dystrophin pre-mRNA resulting in the exclusion of this exon during mRNA processing in patients with genetic variants that are amenable to exon 53 skipping. As a result, viltolarsen, via exon 53 skipping, is

Antisense Oligonucleotide Therapy for Duchenne Muscular Dystrophy

intended to enable the production of an internally truncated dystrophin protein in patients with genetic variants amenable to exon 53 skipping.

Casimersen is an antisense oligonucleotide of the PMO subclass. It binds to exon 45 of dystrophin pre-mRNA resulting in the exclusion of this exon during mRNA processing in patients with genetic variants that are amenable to exon 45 skipping. As a result, casimersen, via exon 45 skipping, is intended to enable the production of an internally truncated dystrophin protein in patients with genetic variants amenable to exon 45 skipping.

The current standard of pharmacotherapy for DMD 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.

Regulatory Status

In September 2016, eteplirsen (Exondys 51™; Sarepta Therapeutics) was approved by the U.S. Food and Drug Administration through the orphan drug status process for use in Duchenne muscular dystrophy (DMD) patients who have a confirmed variant of the *DMD* 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 three years after 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.

In December 2019, golodirsen (Vyondys 53™; Sarepta Therapeutics) was approved by the FDA through the orphan drug status process for use in DMD patients who have a confirmed variant of the *DMD* 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 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.

In August 2020, viltolarsen (Viltepso™; NS Pharma) was approved by the FDA through the orphan drug status process for use in DMD patients who have a confirmed variant of the *DMD* 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 some patients treated with viltolarsen. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

In February 2021, casimersen (Amondys 45™; Sarepta Therapeutics) was approved by the FDA through the orphan drug status process for use in DMD patients who have a confirmed variant of the *DMD* 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 patients treated with casimersen. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

Antisense Oligonucleotide Therapy for Duchenne Muscular Dystrophy

The use of eteplirsen, golodirsen, viltolarsen, and casimersen are considered investigational for all indications including treatment of Duchenne muscular dystrophy. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Antisense Oligonucleotide Therapy for Duchenne Muscular Dystrophy is covered

Not applicable.

When Antisense Oligonucleotide Therapy for Duchenne Muscular Dystrophy is not covered

The use of eteplirsen is considered investigational for all indications including treatment of Duchenne muscular dystrophy.

The use of golodirsen is considered investigational for all indications including treatment of Duchenne muscular dystrophy.

The use of viltolarsen is considered investigational for all indications including treatment of Duchenne muscular dystrophy.

The use of casimersen is considered investigational for all indications including treatment of Duchenne muscular dystrophy.

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.

The recommended dose of golodirsen is 30 mg/kg of body weight administered once weekly as a 35- to 60-minute intravenous infusion.

The recommended dose of viltolarsen is 80 mg/kg of body weight administered once weekly as a 60-minute intravenous infusion.

The recommended dose of casimersen is 30 mg/kg of body weight administered once weekly as a 35- to 60-minute intravenous infusion.

For individuals with a confirmed variant of the *DMD* gene that is amenable to exon 51 skipping who receive eteplirsen, the evidence includes a randomized controlled trial (RCT) and its open-labelled follow-up study, and an 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 and its open-labelled follow-up, no formal sample size calculations were conducted. A sample size of 12 total patients was selected with 4 patients 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 patients and placebo-treated patients at week 48. While eteplirsen treatment resulted in

Antisense Oligonucleotide Therapy for Duchenne Muscular Dystrophy

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 patients 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 DMD 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 DMD amenable to 51 skipping. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with a confirmed variant of the *DMD* gene that is amenable to exon 53 skipping who receive golodirsen, the evidence includes a RCT dose-titration and its open-label follow-up study (NCT02310906). Relevant outcomes are disease-specific survival, change in disease status, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. Twelve children with DMD who had confirmed dystrophin gene deletions amenable to exon 53 skipping were included in the preliminary RCT to assess safety, tolerability, and dose titration. This was followed by an open-label follow-up study that included the original 12 RCT patients and an additional 13 treatment-naïve patients with DMD amenable to exon 53 skipping (n=25). At study enrollment, patients had a median age of 8 years and were on a stable dose of corticosteroids for at least 6 months. Patients received a weekly intravenous infusion of golodirsen 30 mg/kg. After 48 weeks or more of treatment, the mean dystrophin level increased from 0.1% (SD 0.07) of normal at baseline to 1.02% (SD 1.03) of normal by week 48. No clinical benefit was reported. The FDA is requiring the manufacturer to show that golodirsen has clinical benefit (i.e., improved motor function) in an ongoing trial. In summary, the clinical benefit of treatment for DMD with golodirsen, including improved motor function, has not been demonstrated. Establishing a clinical benefit is necessary in ongoing clinical trials. The most frequently reported adverse reactions in clinical trials were headache, fever, cough, vomiting, abdominal pain, nasopharyngitis, and nausea. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with a confirmed variant of the *DMD* gene that is amenable to exon 53 skipping who receive viltolarsen, the evidence includes a 2-period multicenter study which consists of a part 1 randomized, double-blind 4-week safety and tolerability study followed by a part 2 open-label 20-week efficacy and safety study (NCT02740972). Relevant outcomes are disease-specific survival, change in disease status, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. Sixteen children with DMD who had confirmed dystrophin gene deletions amenable to exon 53 skipping were included in the study. At study enrollment, ambulatory male patients had a median age of 7 years and were on a stable dose of corticosteroids for at least 3 months. In patients who received a weekly intravenous infusion of viltolarsen 80 mg/kg (n=8), mean dystrophin levels increased from 0.6% (SD 0.8) of normal at baseline to 5.9% (SD 4.5) of normal by week 25, with a mean change in dystrophin of 5.3% (SD 4.5) of normal levels (p=0.01) and median change from baseline of 3.8%. No clinical benefit was reported. 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 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

Antisense Oligonucleotide Therapy for Duchenne Muscular Dystrophy

patients with Duchenne muscular dystrophy amenable to 53 skipping. The evidence is insufficient to determine the effects of the technology on health outcomes.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 96365, C9399, J1427, J1428, J1429, J3490, J3590

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

Prescribing Label: EXONDYS 51 (eteplirsen) injection, for intravenous use. Sarepta Therapeutics, Inc. http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/206488lbl.pdf . Accessed February 15, 2017.

Accelerated Approval Letter to Sarepta Therapeutics: NDA 206488. 2016, September 19; https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2016/206488Orig1s000ltr.pdf . Accessed February 15, 2017.

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.27, 12/8/2016

Specialty Matched Consultant Advisory Panel 10/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.27, 12/14/2017

Specialty Matched Consultant Advisory Panel 10/2018

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.27, 12/13/2018

Specialty Matched Consultant Advisory Panel 10/2019

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.27, 12/12/2019

Sarepta Therapeutics, Inc. Vyondys 53 (golodirsen) injection for intravenous use. Highlights of prescribing information. December 2019. Available at: [https://www.vyondys53.com/Vyondys53_\(golodirsen\)_Prescribing_Information.pdf](https://www.vyondys53.com/Vyondys53_(golodirsen)_Prescribing_Information.pdf). Last accessed March 2020.

Medical Director review 3/2020

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.27, 3/12/2020

NS Pharma, Inc. Viltepsa (viltolarsen) injection for intravenous use. Highlights of prescribing information. August 2020. Available at: <https://www.viltepsa.com/prescribing-information>. Last accessed September 2020.

Antisense Oligonucleotide Therapy for Duchenne Muscular Dystrophy

U.S. Food and Drug Administration. FDA approves targeted treatment for rare Duchenne muscular dystrophy mutation. Available at: <https://www.fda.gov/news-events/press-announcements/fda-approves-targeted-treatment-rare-duchenne-muscular-dystrophy-mutation#:~:text=Today%2C%20the%20U.S.%20Food%20and,amenable%20to%20exon%2053%20skipping.> Last accessed September 2020.

Medical Director review 9/2020

Specialty Matched Consultant Advisory Panel 10/2020

Blue Cross NC Pharmacy and Therapeutics Committee 1/2021

Sarepta Therapeutics, Inc. Amondys 45 (casimersen) injection for intravenous use. Highlights of prescribing information. February 2021. Available at: [https://www.amondys45.com/Amondys45_\(casimersen\)_Prescribing_Information.pdf](https://www.amondys45.com/Amondys45_(casimersen)_Prescribing_Information.pdf). Last accessed March 2021.

Policy Implementation/Update Information

For Policy Titled: “Eteplirsen fo Duchenne Muscular Dystrophy”

- 3/31/17 New policy developed. The use of eteplirsen is considered investigational for all indications including treatment of Duchenne muscular dystrophy. (sk)
- 12/29/17 Specialty Matched Consultant Advisory Panel review 10/25/2017. Code J1428 added to Billing/Coding section for effective date 1/1/2018. Code C9484 deleted effective 12/31/2017. (sk)
- 1/26/18 Reference added. The word “mutation” changed to the word “variant” throughout the policy. (sk)
- 11/9/18 Specialty Matched Consultant Advisory Panel review 10/24/2018. (krc)
- 10/29/19 Reference added. Specialty Matched Consultant Advisory Panel review 10/16/2019. (krc)

For Policy Re-titled: “Antisense Oligonucleotide Therapy for Duchenne Muscular Dystrophy”

- 3/10/20 Policy title revised from “Eteplirsen for Duchenne Muscular Dystrophy” to “Antisense Oligonucleotide Therapy for Duchenne Muscular Dystrophy”. Added golodirsen (Vyondys 53) to policy with the following policy statement: “the use of golodirsen is considered investigational for all indications including treatment of Duchenne muscular dystrophy.” Updated Description and Policy Guidelines sections to include description and evidence for golodirsen. Other minor typographical edits and additions made for clarity. Added HCPCS codes C9399, J3490, and J3590 to Billing/Coding section. References added. Medical Director review 3/2020. (krc)
- 6/30/20 Added HCPCS code J1429 to Billing/Coding section and deleted codes C9399, J3490, and J3590 effective 7/1/2020. (krc)
- 10/13/20 Added viltolarsen (Viltepso) to policy with the following policy statement: “the use of viltolarsen is considered investigational for all indications including treatment of Duchenne muscular dystrophy.” Updated Description and Policy Guidelines sections to include description and evidence for viltolarsen. Other minor typographical edits and additions

Antisense Oligonucleotide Therapy for Duchenne Muscular Dystrophy

made for clarity. Added HCPCS codes C9399, J3490, and J3590 to Billing/Coding section. References added. Medical Director review 9/2020. (krc)

11/10/20 Specialty Matched Consultant Advisory Panel review 10/21/2020. (krc)

12/31/20 Added HCPCS code C9071 to Billing/Coding section effective 1/1/2021. (krc)

3/31/21 Added casimersen (Amondys 45) to policy with the following policy statement: “the use of casimersen is considered investigational for all indications including treatment of Duchenne muscular dystrophy.” Updated Description and Policy Guidelines sections to include description and dosing for casimersen. Added HCPCS codes C9399, J3490, and J3590 to Billing/Coding section for casimersen. Added HCPCS code J1427 for viltolarsen to Billing/Coding section effective 4/1/2021, and deleted code C9071 termed 3/31/2021. Reference added. Blue Cross NC Pharmacy and Therapeutics Committee 1/5/2021. (krc)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.