Policy Number	**RX501.129**
Policy Effective Date	**02/15/2025**

Viltolarsen

Table of Contents

Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For Illinois only: Illinois Public Act 103-0458 [Insurance Code 215 ILCS 5/356z.61] (HB3809 Impaired Children) states all group or individual fully insured PPO, HMO, POS plans amended, delivered, issued, or renewed on or after January 1, 2025 shall provide coverage for therapy, diagnostic testing, and equipment necessary to increase quality of life for children who have been clinically or genetically diagnosed with any disease, syndrome, or disorder that includes low tone neuromuscular impairment, neurological impairment, or cognitive impairment.

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as

safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Viltepso™ (viltolarsen) for the treatment of Duchenne muscular dystrophy **is considered not medically necessary** as a clinical benefit has not been established.

Viltepso™ (viltolarsen) for the treatment of all other indications **is considered experimental, investigational and/or unproven.**

Policy Guidelines

None.

Description

Duchenne muscular dystrophy (DMD) 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 DMD 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 ribonucleic acid (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. Antisense oligonucleotides have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of DMD, each targeting a specific exon. Viltolarsen targets skipping of exon 53.

Background

Duchenne Muscular Dystrophy (DMD)

DMD is an X-linked, recessive disorder that occurs in approximately 1 in 3600 to 6000 males. It primarily affects males. However, a small number of females are also affected, but they are usually asymptomatic or only present with a mild form of the disease. (1) 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 5 years. (2) Symptoms of DMD

include motor difficulties such as difficulty running, jumping, walking upstairs, and an unusual waddling gait. Some improvement in symptoms may be observed from 3 to 6 years of age, although 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.

DMD occurs because 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 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. (3) 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.

Management of individuals with a confirmed variant of DMD involves treatment with corticosteroids. Treatment is initiated once patients reach a plateau of motor skill development, generally at ages 4 to 6 years, but before the 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. (1)

Regulatory Status
In August 2020, viltolarsen (Viltepso; Nippon Shinyaka Co.) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with Viltepso.

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. (4, 5)

Rationale

The effect of Viltepso™ on dystrophin production was evaluated in one study in Duchenne muscular dystrophy (DMD) patients with a confirmed mutation of the DMD gene that is

amenable to exon 53 skipping (Study 1; NCT02740972). Study 1 was a multicenter, 2-period, dose-finding study conducted in the United States and Canada. During the initial period (first 4 weeks) of Study 1, patients were randomized (double blind) to Viltepso or placebo. All patients then received 20 weeks of open-label Viltepso 40 mg/kg once weekly (0.5 times the recommended dosage) (N=8) or 80 mg/kg once weekly (N=8). Study 1 enrolled ambulatory male patients 4 years to less than 10 years of age (median age 7 years) on a stable corticosteroid regimen for at least 3 months. Efficacy was assessed based on change from baseline in dystrophin protein level (measured as percentage of the dystrophin level in healthy subjects, i.e., % of normal) at Week 25. Muscle biopsies (left or right biceps brachii) were collected from patients at baseline and following 24 weeks of Viltepso treatment and analyzed for dystrophin protein level by Western blot normalized to myosin heavy chain (primary endpoint) and mass spectrometry (secondary endpoint).

In patients who received Viltepso 80 mg/kg once weekly, 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) as assessed by validated Western blot (normalized to myosin heavy chain); the median change from baseline was 3.8%. All patients demonstrated an increase in dystrophin levels over their baseline values. As assessed by mass spectrometry (normalized to filamin C), mean dystrophin levels increased from 0.6% (SD 0.2) of normal at baseline to 4.2% (SD 3.7) of normal by Week 25, with a mean change in dystrophin of 3.7% (SD 3.8) of normal levels (nominal p=0.03, not adjusted for multiple comparisons); the median change from baseline was 1.9%. (4-6)

Kidney toxicity was not observed in clinical studies with Viltepso, although it was observed in animals who had received viltolarsen. Therefore, the FDA noted that kidney function should be monitored in patients taking Viltepso. Because serum creatinine may not be a reliable measure of kidney function in DMD patients, other measures should be monitored. Serum cystatin C, urine dipstick, and urine protein-to-creatinine ratio should be measured before starting Viltepso. Urine dipstick should be monitored every month; serum cystatin C and urine protein-to-creatinine ratio should be monitored every 3 months. In the event of persistent elevation in serum cystatin C or proteinuria, the patient should be referred to a pediatric nephrologist for further evaluation. (4, 5)

The results of an extension trial, NCT03167255, were published in May 2022. In this trial, Clemens et al. hoped to evaluate the long-term efficacy and safely of viltolarsen in the treatment of 16 patients with DMD amenable to exon 53 skipping therapy. The results of the trial showed time to stand from supine and time to run/walk 10 meters showed stabilization from baseline through week 109 for viltolarsen-treated participants whereas the historical control group showed decline (statistically significant differences for multiple timepoints). Safety was similar to that observed in the previous 24-week trial, which was predominantly mild. There were no treatment-related serious adverse events and no discontinuations reported. Based on these results at over 2 years, the authors concluded viltolarsen can be a new treatment option for patients with DMD amenable to exon 52 skipping. The authors note limitations in this study, which include the fact that only 8%-10% of individuals with DMD have

a variant amenable to exon 53 skipping. They also used an historical control group (group-level matched) rather than a placebo arm. They state: "The use of an historical control group, although less rigorous than a randomized, placebo-controlled study design, is appropriate for a Phase 2 trial in a rare disease with a surrogate primary outcome. However, an analysis of the consistency of change in 6-minute walk distance in DMD using group-matched DMD natural history data from 5 separate natural history datasets found that external controls were not different from placebo controls drawn from placebo datasets included in 6 randomized, blinded DMD treatment studies encompassing 4 sets of eligibility criteria. While this study did not use patient-level matching due to the small patient population size in the DMD historical control group; it used group-level matching, which included age, geographic location, ambulatory ability, and glucocorticoid use. (7)

In 2023, Clemens et al. (8) phase 2, open-label, 4-year extension study examined > 4 years of functional outcomes in viltolarsen-treated patients compared to a historical control group. This 192-week extension study (NCT03167255) evaluated the efficacy and safety of viltolarsen in individuals aged 4 to < 10 years at baseline with DMD amenable to exon 53 skipping. All 16 individuals from the initial 24-week study enrolled into this extension study. Timed function tests were compared to the CINRG DNHS group. All participants received glucocorticoid treatment. The primary efficacy outcome was time to stand from supine. Secondary efficacy outcomes included additional timed function tests. Safety was continuously assessed. For the primary efficacy outcome, viltolarsen-treated patients showed stabilization of motor function over the first 2 years and significant slowing of disease progression over the following 2 years compared with the CINRG DNHS control group which declined. Viltolarsen was well tolerated, with most reported treatment-emergent adverse events being mild or moderate. No participants discontinued the drug during the study. Based on the results of this 4-year extension study, the authors believe viltolarsen can be an important treatment strategy for DMD patients amenable to exon 53 skipping.

To confirm the clinical findings, a Phase 3 randomized, double-blind, placebo-controlled, multi-center study (NCT04060199; RACER53) to assess the efficacy and safety of viltolarsen in boys with DMD who are able to walk independently without assistive devices is being conducted.

UpToDate

In 2023, UpToDate (9) evaluated published literature related to disease-modifying treatments for DMD. UpToDate states that genetic therapies that involve exon skipping (i.e., viltolarsen) may modestly increase dystrophin levels, although it is uncertain if patients benefit from treatment.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Enrollment	Completion Date

NCT04768062	Study to Assess the Safety and Efficacy of Viltolarsen in Ambulant Boys With DMD (RACER53-X)	74	June 2026
NCT04956289	Study to Assess the Safety, Tolerability, and Efficacy of Viltolarsen in Ambulant and Non-Ambulant Boys With DMD (Galactic53)	20	September 2023 (Completed, no results posted)
NCT04687020	Long-term Use of Viltolarsen in Boys With Duchenne Muscular Dystrophy in Clinical Practice (VILT-502);	9	Oct 2032 (Active, not recruiting)
NCT04060199	Study to Assess the Efficacy and Safety of Viltolarsen in Ambulant Boys With DMD (RACER53);	74	Dec 2024

Summary of Evidence

For individuals with a confirmed variant of the Duchenne muscular dystrophy (DMD) 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% (±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 DMD, 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 DMD amenable to 53 skipping. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome therefore is considered not medically necessary.

Practice Guidelines and Position Statements

Centers for Disease Control and Prevention

In 2010, the U.S. Centers for Disease Control and Prevention convened a DMD Care Considerations Working Group. In 2010, the Working Group developed care recommendations and updated them in 2018. (10) The 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 DMD. The Working Group did not make recommendations on the use of Viltepso™ (viltolarsen). (10, 11)

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 DMD. (12) For patients with DMD, the Association recommended the use of glucocorticoids, among other medications. The statement does not address the use of Viltepso™ (Viltolarsen).

American Academy of Neurology

In 2016, the American Academy of Neurology (AAN) published an updated practice guideline on the use of corticosteroids for the treatment of DMD. (13) The AAN does not discuss the use of Viltepso™ (Viltolarsen) FOR DMD.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J1427, C9399, J3490, J3590

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

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 (Nov 21, 2022). Available at <https://www.cdc.gov> (accessed January 4, 2024).
3. Falzarano MS, Scotton C, Passarelli C, et al. Duchenne muscular dystrophy: from diagnosis to therapy. Molecules. Oct 07 2015; 20(10):18168-18184. PMID 26457695
4. Food and Drug Administration (FDA) Prescribing Label: Viltepso™ (viltolarsen) injection, for intravenous use (March 2021). Available at <https://www.accessdata.fda.gov> (accessed January 4, 2024).

5. Food and Drug Administration (FDA) Prescribing Label: Viltepso™ (viltolarsen) injection. (August 2020). Available at <https://www.accessdata.fda.gov> (accessed January 5, 2024).
6. Clemens P, Rao V, Connolly A, 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
7. Clemens PR, Rao VK, Connolly AM, et al. Long-term functional efficacy and safety of viltolarsen in patients with Duchenne Muscular Dystrophy. J Neuromuscul Dis. 2022; 9(4):493-501. PMID 35634851
8. Clemens PR, Rao VK, Connolly AM, et al. Efficacy and safety of viltolarsen in boys with Duchenne Muscular Dystrophy: results from a phase 2, open label, 4-year extension study. J Neuromuscul Dis. 2023; 10(3):439-447. PMID 37005891
9. Darris B. Duchenne and becker muscular systropy: Glococorticoid and disease modifying treatment. In: UpToDate, Dashe J. (Ed), UpToDate, Waltham, MA. Available at <http://www.uptodate.com> (accessed January 5, 2024).
10. 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
11. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 3: primary care, emergency management, psychosocial care, and transitions of care across the lifespan. Lancet Neurol. May 2018; 17(5):445-455. PMID 29398641
12. 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
13. Gloss D, Moxley R, 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):465-472. PMID 26833937

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
02/15/2025	Reviewed. No changes.

03/15/2024	Document updated with literature review. Coverage unchanged. Added references 4, 8, 9; others removed or revised.
03/15/2023	Reviewed. No changes.
10/15/2022	Document updated with literature review. Coverage unchanged. Reference 6 added; others removed or revised.
11/01/2021	Reviewed. No changes.
05/01/2021	New medical document. Viltepso™ (Viltolarsen) for the treatment of Duchenne muscular dystrophy is considered not medically necessary as a clinical benefit has not been established. Viltepso™ (Viltolarsen) for the treatment of all other indications is considered experimental, investigational and/or unproven.