

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Muscular Dystrophy – Viltepso Utilization Management Medical Policy

- Viltepso™ (viltolarsen intravenous infusion – Nippon Shinyaku)

REVIEW DATE: 08/21/2024

OVERVIEW

Viltepso, an antisense oligonucleotide, is indicated for the treatment of **Duchenne muscular dystrophy (DMD)** in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping.¹ This indication was granted accelerated approval based on an increase in dystrophin in skeletal muscle observed in patients treated with Viltepso. The prescribing information notes that continued FDA approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.

Viltepso is an antisense oligonucleotide designed to bind to exon 53 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 53 skipping.¹ These patients represent up to 10% of all patients with DMD.² This genetic manipulation intends to restore the reading frame of the resulting mRNA. The result would be production of a shortened, but partially functional dystrophin protein as seen in less severe forms of muscular dystrophy (e.g., Becker muscular dystrophy). Of note, the reading frame of certain deletions (e.g., exon 52 deletions) can be restored by skipping either exon 51 or exon 53.³ Approximately 8% of mutations are amenable to skipping exon 53 with Viltepso but are not amenable to skipping of exon 51.

Guidelines

Viltepso and other exon 53 skipping therapies are not addressed in guidelines for DMD. There are guidelines for the diagnosis and management of DMD available from the DMD Care Considerations Working Group (2018).⁴ Genetic testing for a DMD mutation in a blood sample is always required. By fully characterizing the mutation, the predicted effect on the reading frame can be identified, which is the major determinant of phenotype and will determine eligibility for mutation-specific clinical trials. In patients with no mutation identified but with signs/symptoms of DMD, a muscle biopsy is clinically indicated. Glucocorticoids slow decline in muscle strength and function in DMD. Use of corticosteroids reduces the risk of scoliosis and stabilizes pulmonary function. Continued treatment after the patient loses ambulation provides a reduction in the risk of progressive scoliosis and stabilization of pulmonary function tests. Therefore, glucocorticoids should be considered for all patients with DMD. Exondys® 51 (eteplirsen intravenous infusion) is mentioned as an emerging product, approved by an accelerated pathway for those with a mutation in the dystrophin gene amenable to exon 51 skipping.

POLICY STATEMENT

The prescribing information for Viltepso states that approval is based on dystrophin production in a limited number of patients (n = 8 treated with the approved dose) with DMD, but approval may be contingent upon a confirmatory trial. Due to inadequate clinical efficacy data, **approval is not recommended** for Viltepso.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Viltepsa is not recommended in the following situations:

- 1. Duchenne Muscular Dystrophy (DMD).** Approval is not recommended due to the unclear benefit of Viltepsa and lack of clinical efficacy data. Shortcomings of the clinical data with Viltepsa are numerous. Although the pivotal study demonstrated a measurable increase in dystrophin levels, the significance of this small change has not yet been correlated with a clinical benefit. Data from the pivotal study did not provide any information to determine if Viltepsa provides a benefit in regard to cardiac and respiratory complications which contribute greatly to morbidity and mortality in DMD. The pivotal data are also lacking robust functional outcomes related to motor function. Viltepsa has not been proven to alter or delay the disease progress in patients with DMD amenable to exon 53 skipping. A systematic review and meta-analysis of other exon skipping therapies (i.e., Exondys 51, drisapersen) does not show benefit of these therapies for DMD.⁵ The prescribing information notes that continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.¹ FDA has required a post-marketing trial to verify clinical efficacy of Viltepsa. Thus, patients are being recruited for the Phase III RACER53 study, to further evaluate safety and efficacy of Viltepsa in 74 ambulatory patients with DMD.⁹ The estimated primary completion date for this study is October 2025.

Viltepsa is under evaluation in one ongoing Phase II pivotal study in patients with DMD amenable to exon 53 skipping.⁶ The primary endpoint is the effect of Viltepsa on dystrophin as a surrogate outcome marker. Functional outcomes were among the secondary endpoints and were compared with a natural history cohort controlled for age, functional status, geographic location, and glucocorticoid treatment status. In this pivotal study (n = 16), the proportion of normal dystrophin protein level was higher at Week 25 (0.6% of normal at baseline vs. 5.9% of normal at Week 24 biopsy). Some functional outcomes were significantly improved from baseline with Viltepsa vs. the natural history cohort (time to run/walk 10 meters [0.23 meters/second vs. -0.04 meters/second], time to stand from supine [-0.19 seconds vs. 0.66 seconds], and distance on the 6-minute walk test [28.9 meters vs. -65.3 meters]). However, velocity in the time to stand from supine test, time to climb 4 stairs test, North Star Ambulatory Assessment test, and measures of muscle strength by isometric testing were not significantly different from the control group. Data from the long-term extension (out to 109 weeks) of the pivotal trial have been published.⁷ All 16 patients who completed the Phase II trial continued into the long-term extension. Functional outcomes (time to stand and time to run/walk 10 meters) were maintained in the Viltepsa group over 109 weeks while they were worsened in the natural history cohort. The time to climb 4 stairs was not significantly different from the natural history cohort over the 109 weeks. Final results from the 192-week long-term extension study (4 years post-treatment) showed stabilization of motor function over the first 2 years for the primary endpoint of time to stand and significant slowing of motor function loss (compared to historical control groups) over the following 2 years.⁸ Similar results were observed with time to run/walk. Time to climb results were not significantly different between Viltepsa and control groups.

- 2.** Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Viltepsio™ intravenous infusion [prescribing information]. Paramus, NJ: Nippon Shinyaku; March 2021.
2. van Deutekom JC, Bremmer-Bout M, Janson AA, et al. Antisense-induced exon skipping restores dystrophin expression in DMD patient derived muscle cells. *Hum Mol Genet.* 2001;10(15):1547-1554.
3. Bladen CL, Salgado D, Monges S, et al. The TREAT-NMD DMD Global Database: analysis of more than 7,000 Duchenne muscular dystrophy mutations. *Hum Mutat.* 2015;36(4):395-402.
4. 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.* 2018;17(3):251-267.
5. Shimizu-Motohashi Y, Murakami T, Kimura E, et al. Exon skipping for Duchenne muscular dystrophy: a systematic review and meta-analysis. *Orphanet J Rare Dis.* 2018;13(1):93.
6. 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. *JAMA Neurology.* 2020;77(8):982-991.
7. Clemens PR, Rao VK, Connolly AM, et al. Long-term functional efficacy and safety of viltolarsen in patients with Duchenne muscular dystrophy. *J Neuromusc Dis.* 2022;9:490-501.
8. Clemens PR, Rao VK, Connolly AM, et al. Efficacy and safety of viltolarsen in boys with Duchenne muscular dystrophy: results from the phase 2, open-label, 4-year extension study. *J Neuromusc Dis.* 2023;439-447.
9. NS Pharma, Inc. Study to assess the safety and efficacy of viltolarsen in ambulant boys with DMD (RACER53-X). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2024 August 19]. Available at: <https://www.clinicaltrials.gov/study/NCT04768062?intr=viltolarsen&rank=1>. NLM Identifier: NCT04768062.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes	08/30/2023
Annual Revision	No criteria changes	08/21/2024