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Next Review Due By: 04/2024
Policy Number: C20585-A

Viltepso (viltolarsen) NC

PRODUCTS AFFECTED

Viltepso (viltolarsen)

COVERAGE POLICY

Coverage for services, procedures, medical devices, and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.
This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Duchenne muscular dystrophy (DMD).

REQUIRED MEDICAL INFORMATION:
Viltepso (viltolarsen) is considered not medically necessary for all indications, including DMD, due to insufficient evidence of therapeutic value since clinical benefit has not been established. Viltepso (viltolarsen) was granted †accelerated approval by the FDA. While the observed increase in dystrophin production associated with viltolarsen treatment is reasonably likely to predict a clinical benefit in this patient population, a confirmed clinical benefit of this drug has not been established.

†*While the accelerated approval pathway makes Viltepso available to DMD patients based on initial data, the drug's clinical benefit must be established from the ongoing confirmatory clinical trial*

Confirmatory Trial
As part of its accelerated approval, the FDA will require that the manufacturer (NS Pharma) conduct a confirmatory clinical trial to show that treatment with the drug improves time to stand in patients with DMD amenable to exon 53 skipping. The continued approval of Viltepso may be contingent on confirmation of a clinical benefit in a confirmatory trial: A phase 3 randomized placebo-controlled double-blind trial (Phase

3RACER53 trial) continues to study the safety and efficacy of Viltepso in ambulant boys with DMD. 74 participants are anticipated; the estimated primary completion date is November 2024. An extension of the pivotal phase II trial is ongoing

FDA-approved indication does not, in itself, dictate coverage. Molina coverage Policy may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare. The covered FDA-approved indications are conditions that are considered medically necessary; however, it is not inclusive of all conditions which may be approved by the Medical Reviewer. At the discretion of the Medical Director and on a case-by-case basis, Molina Healthcare may consider authorization of the biologic therapy addressed in this Policy for members with exceptional circumstances and for members with severe disease who may fall outside of the defined criteria.

CONTINUATION OF THERAPY:
N/A

DURATION OF APPROVAL:
N/A

PRESCRIBER REQUIREMENTS:
N/A

AGE RESTRICTIONS:
N/A

QUANTITY:
N/A

PLACE OF ADMINISTRATION:
N / A

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Intravenous

DRUG CLASS:
Muscular Dystrophy Agents

FDA-APPROVED USES:
Treatment of Duchenne muscular dystrophy (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. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:

Appendix 1: Duchenne Muscular Dystrophy (DMD)

Muscular dystrophy includes a group of genetic disorders that cause muscle weakness and progressive disability. Duchenne muscular dystrophy (DMD) is the most common and progresses most rapidly.
Duchenne muscular dystrophy (DMD)

- A rare genetic disorder characterized by progressive muscle deterioration and weakness
- An X-chromosome-linked disease recessive disorder caused by mutations (mainly deletions) in the dystrophin gene that lead to an absence or defect in the dystrophin protein (a protein that that protects muscles from deterioration). Dystrophin is essential for maintenance of myocyte integrity and helps keep muscle cells intact. Dystrophin is located primarily in skeletal and heart muscle.
- As males have only one X chromosome, and therefore one single copy of the dystrophin gene, they have a much higher probability of developing DMD. A small number of females are also affected but remain asymptomatic and only rarely present with a mild form of the disease.
- The most common type of muscular dystrophy; DMD is caused by an absence of dystrophin, a protein that helps keep muscle cells intact
- Based on population studies, the prevalence of DMD in the US is estimated to be 0.4 per 10,000 males, resulting in approximately 6,000 affected people in the US (Romitti, 2015)
- Associated with complete inability to produce functional dystrophin protein
- Affected children with DMD typically develop symptoms in early childhood around 3-5 years old, experiencing progressive muscle weakness and deterioration. Patients with DMD progressively lose the ability to perform activities independently and usually become non-ambulatory by their early teenage years and require the use of a wheelchair.
- As the disease progresses, life-threatening heart and respiratory conditions can occur. Patients typically succumb to the disease in their 20s or 30s; however, disease severity and life expectancy vary.
- In absence of treatment, the patient experiences:

wheelchair dependence before age 13 years death occurs by, or around, age 20 years Prognosis of DMD

- Death occurs around age 20 in absence of treatment and is usually due to cardiac or respiratory failure
- Disease progression in patients with DMD Scoliosis is frequent after loss of

ambulation Risk for cardiomyopathy increases with age in absence of
ventilatory intervention

Treatment Overview: Pharmacologic Agents/Conventional Therapy
There is no curative therapy, but management of disease manifestations can prolong survival and improve quality of life. A multidisciplinary team is required for management of patient with DMD and treatment options for DMD predominantly focus on management of symptoms and secondary complications.

Goals of management for DMD

- Preserve strength, ambulation, and ventilatory and cardiac function
- Minimize of steroid complications where applicable
- Prevent and treat complications including contractures, scoliosis, ventilatory function impairment or failure, and cardiomyopathy
- Determine and arrange appropriate school environment and manage family stressors

Other pharmacologic therapies for DMD are primarily aimed at the management of comorbidities such as cardiomyopathy, osteoporosis, pain management, and respiratory failure. These treatment options include angiotensin-converting-enzyme (ACE) inhibitors, beta-blockers, calcium and vitamin D supplements, muscle relaxants, and non-steroidal anti-inflammatory drugs.

- Corticosteroids

DMD Care Considerations Working Group consensus guidelines urge consideration of glucocorticoid therapy(prednisone or deflazacort) for all patients with DMD (optimal dose ranges not established) Goal in the ambulatory child is to preserve ambulation and minimize later respiratory, cardiac, and orthopedic complications
Goal of continuing glucocorticoid therapy after loss of ambulation is to preserve upper limb strength, reduce

scoliosis progression, and delay declines in respiratory and cardiac function
Generally used to preserve ambulation and minimize complications in patients with DMD In ambulatory patients, recommended if motor skills have plateaued or begun to decline
In non-ambulatory patients, glucocorticoids often continued if already started while ambulatory, but limited evidence regarding starting glucocorticoids
Daily dosing preferred over alternative regimens (alternate day, high-dose weekend, or 10-day cycles)Monitor and manage side effects associated with chronic steroid therapy

- Vitamin D and calcium supplementation suggested to manage bone health in patients with DMD
- Respiratory care including airway clearance techniques, nocturnal ventilatory support, daytime non-invasive ventilation, and tracheostomy may be indicated/desired as disease progresses
- For management of cardiac dysfunction, consider:

Diuretics, angiotensin-converting enzyme (ACE) inhibitors, and/or beta blockers to treat manifestations of cardiac dysfunction
Anticoagulation therapy in patients with severe cardiac dysfunction to prevent systemic thromboembolic events

Appendix 2: Guidelines

American Academy of Neurology guideline update on corticosteroid treatment of Duchenne dystrophy can be found in Neurology 2016 Feb 2;86(5):465 or at National Guideline Clearinghouse 2016 Jun 6:50008

American Academy of Pediatrics (AAP) policy statement on cardiovascular health supervision for individuals affected by Duchenne or Becker muscular dystrophy can be found in Pediatrics 2005Dec;116(6):1569 full-text, reaffirmed 2008 Dec, commentary can be found in Pediatrics 2006 May;117(5):1864 full-text

United States expert consensus guideline on diagnosis and management of Duchenne muscular dystrophy

- Part 1: Diagnosis, pharmacological and psychosocial management can be found in Lancet Neurol2010 Jan;9(1):77 PDF or at National Guideline Clearinghouse 2010 Aug 2:15644
- Part 2: Implementation of multidisciplinary care can be found in Lancet Neurol 2010 Feb;9(2):177 PDF or at National Guideline Clearinghouse 2010 Aug 2:15645

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

The best available evidence is limited to a single published report on a phase 2 dose-finding study (NCT02740972; Clemens et al., 2020). This multicenter 2-period randomized clinical trial of low-dose (40 mg/kg per week) and high-dose (80 mg/kg per week) viltolarsen in participants with Duchenne muscular dystrophy (DMD) amenable to exon 53 skipping enrolled 8 participants in each dose cohort. In both cohorts, participant screening, clinical assessments, and a baseline skeletal muscle biopsy were performed before the first administration of the study drug.

Eligible participants were boys aged 4 to 9 years who were ambulatory, on a stable dose of glucocorticoids for 3 months prior to enrollment, and able to complete time to stand from supine, time to run/walk 10 meters, and time to climb 4 stairs assessments at screening. Of the 16 participants, 15 (94%) were white, and the mean (SD) age was 7.4 (1.8) years.

The first study period (the first 4 weeks of treatment) was double-blinded and placebo-controlled. Participants in both dose cohorts were randomized 3:1 to receive viltolarsen or placebo. In each dose cohort, a minimum of 1 week was required between the initial dosing of each of the first 4 participants to monitor for safety. After the fourth participant received the initial dose, the remaining participants could receive treatment.

The second study period began at week 5 for each participant. During this period, all participants received viltolarsen according to their cohort dose for a 20-week open-label treatment period. Following completion of the 24-week treatment period, each participant had a post-treatment skeletal muscle biopsy performed.

All 16 participants competed 24 weeks of treatment.

Disease progression was measured using timed function tests and muscle strength assessments. Comparison of viltolarsen-treated participants with 65 age-matched and treatment-matched natural history controls from CINRG, Cooperative International Neuromuscular Research Group demonstrated evidence of clinical benefit of viltolarsen treatment

Results
After 20 to 24 weeks of treatment:
- 100% of Viltolarsen-treated patients (8/8) showed an increase in dystrophin levels;88% of patients (7/8) showed dystrophin levels of 3% or greater than normal
- A mean increase in dystrophin expression to nearly 6% (5.9%) of normal was observed with Viltepso (80 mg/kg/wk) versus 0.6% at baseline
- Significant drug-induced dystrophin production was seen in both viltolarsen dose cohorts:40 mg/kg per week: mean (range) 5.7% [3.2-10.3] of normal
80 mg/kg per week: mean [range] 5.9% [1.1-14.4] of normal)

Compared with 65 age-matched and treatment-matched natural history controls, all 16 participants treated with viltolarsen showed significant improvements in timed function tests from baseline. The treatment-matched natural history control group demonstrated a decline in timed function tests.
- The time to run/walk 10 meters test significantly improved in viltolarsen-treated participants at weeks 13 and 25 compared with a decline in the natural history control group.: (viltolarsen: 0.23 m/s; control: −0.04 m/s),
- The 6-minute Walk Test (6MWT) showed significant improvement in viltolarsen-treated participants, whereas results from natural history controls declined over the same period: (viltolarsen: 28.9 m; control: −65.3 m)
- Time to stand from supine test and time to climb 4 stairs test displayed improvement or stabilization, but the differences were not significant between viltolarsen treatment and the natural history control group: (viltolarsen: −0.19 s; control: 0.66 s)

Viltolarsen was well tolerated; no treatment-emergent adverse events required dose reduction, interruption, or discontinuation of the study drug. No serious adverse events or deaths occurred during the study.
As with all oligonucleotides, there is potential for immunogenicity. However, both study 1 and 2 demonstrated a lack of observed immunogenicity, which indicates that viltolarsen is not highly immunogenic.

CLINICAL GUIDELINES

No published guidelines were identified that addressed the use of viltolarsen for the treatment of DMD (August 2020)

Related DMD Evidence Reports and Guidelines

The Institute for Clinical and Economic Review (ICER), published an Evidence Report assessing the comparative clinical benefit and value of the corticosteroid deflazacort (Emflaza), and two exon-skipping therapies eteplirsen (Exondys 51™) and golodirsen for the treatment DMD. Viltepso was not included in this review.

ICER noted:
- The exon-skipping therapies, eteplirsen and golodirsen, cannot be assessed for cost- effectiveness because “no persuasive evidence yet exists to demonstrate the clinical effectiveness of either drug.”
- Data for exon-skipping therapies consist primarily of surrogate outcomes (e.g., dystrophin levels) from very small trials that have no validated threshold that defines meaningful clinical improvement. The small increases in dystrophin levels seen in the RCTs are of uncertain clinical significance.
- Both eteplirsen and golodirsen have been shown to increase production of dystrophin, which is deficient in DMD, although dystrophin levels remained very low. The best results were for golodirsen, according to the report; at 48 weeks, the mean level of dystrophin had increased to 1.019 percent of

normal. There is no validated threshold in dystrophin levels associated with meaningful clinical improvement.

- There is found no evidence demonstrating improvements in muscle strength, motor function, ambulation, or pulmonary function.
- No functional outcome results have been reported for golodirsen.
- There was insufficient evidence to judge the net health benefit of adding golodirsen compared with using corticosteroids and supportive care alone.

DUCHENNE MUSCULAR DYSTROPHY CARE CONSIDERATIONS WORKING GROUP
Diagnosis and Management of Duchenne Muscular Dystrophy, Part 1: Diagnosis, and Pharmacological and Psychosocial management (Bushby et al 2010)

- Glucocorticoids are the only medications currently available that slow the decline in muscle strength and function in DMD, which in turn reduces the risk of scoliosis and stabilizes pulmonary function. Cardiac function might also improve, with limited data to date indicating a slower decline in echocardiographic measures of cardiac dysfunction, although these measures are not necessarily predictive of the delay in cardiac symptoms, signs, or cardiac-related mortality.
- The goal of the use of glucocorticoids in the ambulatory child is the preservation of ambulation and the minimization of later respiratory, cardiac, and orthopedic complications, considering the well-described risks associated with chronic glucocorticoid administration. Particular care needs to be taken with such patients in deciding which glucocorticoid to choose, when to initiate treatment, and how best to monitor the child for any problems.
- No generally accepted guidelines exist in the literature about the best time to initiate glucocorticoid therapy in an ambulatory boy with DMD. The panel's opinion is that the timing of initiation of glucocorticoid therapy must be an individual decision, based on functional state and also considering age and pre-existing risk factors for adverse effects (AEs). Initiation of glucocorticoid treatment is not recommended for a child who is still gaining motor skills, especially when he is under 2 years of age.
- The typical boy with DMD continues to make progress in motor skills until approximately age 4 to 6 years, albeit at a slower rate than his peers. The eventual use of glucocorticoids should be discussed with caregivers at this stage, in anticipation of the plateau in motor skills and subsequent decline. Once the plateau phase has been clearly identified, usually at age 4 to 8 years, the clinician should propose initiation of glucocorticoids unless there are substantial reasons (such as major pre-existing risk factors for AEs) to wait until the decline phase. Starting steroids when in the full decline phase or when ambulation is more marginal is still recommended but might be of more limited benefit.
- Prednisone (prednisolone) and deflazacort are believed to work similarly and neither one has a clearly superior effect on altering the decline in motor, respiratory, or cardiac function in DMD. The choice of which glucocorticoid to use depends on legal availability, cost, formulation, and perceived AE profiles. Prednisone is inexpensive and available in tablet and liquid formulations. Where available, deflazacort is more expensive and comes in fewer tablet sizes. Deflazacort might be preferred to prednisone for some patients because of the likely lower risk of weight gain.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Viltepso (viltolarsen) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Viltepso (viltolarsen) include: No labeled contraindications.

OTHER SPECIAL CONSIDERATIONS:

None

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Viltepso SOLN 250MG/5ML

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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: FDA-Approved Uses Contraindications/Exclusions/Discontinuation References	Q2 2023
ANNUAL REVIEW COMPLETED- No coverage criteria changes with this annual review.	Q2 2022
Q2 2022 Established tracking in new format	Historical changes on file