Viltepso® (Viltolarsen)

Policy Number: 2023D0095F
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Coverage Rationale

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Viltepso (viltolarsen) may be covered for the treatment of Duchenne muscular dystrophy (DMD) in patients who meet all of the following criteria:

- For **initial therapy**, **all** of the following:
  - Diagnosis of Duchenne muscular dystrophy by, or in consultation with, a neurologist with expertise in the diagnosis of DMD; **and**
  - Submission of medical records (e.g., chart notes, laboratory values) confirming the mutation of the DMD gene is amenable to exon 53 skipping; **and**
  - **One** of the following:
    - Submission of medical records (e.g., chart notes, laboratory values) confirming that the patient has a 6-Minute Walk Test (6MWT) ≥ 300 meters while walking independently (e.g., without side-by-side assist, cane, walker, wheelchair, etc.) prior to beginning Viltepso therapy; **or**
    - **Both** of the following:
      - Submission of medical records (e.g., chart notes) confirming that the patient is ambulatory **without** needing an assistive device (e.g., without side-by-side assist, cane, walker, wheelchair, etc.); **and**
      - **One** of the following:
        - Patient has achieved a score of greater than 17 on the North Star Ambulatory Assessment (NSAA); **or**
        - Patient has achieved a time to rise from the floor (Gower's test) of less than 7 seconds

    and
  - Viltepso is prescribed by, or in consultation with, a neurologist with expertise in the treatment of DMD; **and**
  - Viltepso dosing for DMD is in accordance with the United States Food and Drug Administration approved labeling; **and**
  - Viltepso is not used concomitantly with other exon skipping therapies for DMD; **and**
  - Initial authorization will be for no more than 6 months
- For **continuation of therapy**, **all** of the following:
  - Patient has previously received Viltepso; **and**
  - Viltepso is prescribed by, or in consultation with, a neurologist with expertise in the treatment of DMD; **and**

- Submission of medical records (e.g., chart notes) confirming that the patient is ambulatory **without** needing an assistive device (e.g., without side-by-side assist, cane, walker, wheelchair, etc.); **and**
- Viltepso dosing for DMD is in accordance with the United States Food and Drug Administration approved labeling; **and**
- Viltepso is not used concomitantly with other exon skipping therapies for DMD; **and**
- Reauthorization will be for no more than 12 months

Viltepso will not be covered for other forms of muscular dystrophy.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J1427	Injection, viltolarsen, 10 mg

Diagnosis Code	Description
G71.01	Duchenne or Becker muscular dystrophy

Background

Duchenne muscular dystrophy (DMD) is an X-linked disease that affects 1 in 3,600-6,000 live male births. DMD occurs as a result of mutations (mainly deletions) in the dystrophin gene. These mutations lead to an absence or a defect of the protein, dystrophin, resulting in progressive muscle degeneration, leading to loss of ambulation and additional respiratory, orthopedic, and cardiac complications. If left untreated, mean age of death is approximately 19 years of age.[2-4]

Viltolarsen is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) subclass. PMOs are synthetic molecules in which the five-membered ribofuranosyl rings found in natural DNA and RNA are replaced by a six-membered morpholino ring. Each morpholino ring is linked through an uncharged phosphorodiamidate moiety rather than the negatively charged phosphate linkage that is present in natural DNA and RNA. Each phosphorodiamidate morpholino subunit contains one of the heterocyclic bases found in DNA (adenine, cytosine, guanine, or thymine).[1]

Viltolarsen is 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. Approximately 8% of DMD patients have out-of frame deletion mutations amenable to exon 53 skipping. Exon skipping is intended to allow for production of an internally truncated dystrophin protein.[1]

Eteplirsen (Exondys 51) was the first PMO approved by the US Food and Drug Administration for treatment of DMD patients with confirmed genetic mutations amenable to exon 51 skipping. Approximately 13% of DMD patients have out-of frame deletion mutations 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 A clinical benefit of eteplirsen has not been established. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.[5]

Golodirsen (Vyondys 53) was the second PMO approved by the US Food and Drug Administration for treatment of DMD patients with confirmed genetic mutations amenable to exon 53 skipping, the same population as viltolarsen. Approximately 8-10 % of DMD patients have out-of frame deletion mutations amenable to exon 53 skipping. This indication was also approved under accelerated approval based on an increase in dystrophin in skeletal muscle. [6]

Casimersen (Amondys 45) is an antisense oligonucleotide that is designed to bind to exon 45 of dystrophin pre-messenger RNA, resulting in exon 45 skipping during messenger RNA processing in patients with amenable deletion mutations of the DMD gene. The FDA granted accelerated approval of casimersen for the treatment of patients with DMD who have a confirmed mutation of DMD that is amenable to exon 45 skipping, which is thought to cause approximately 8 percent of DMD cases.[14]

Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. Refer to the Policy and Procedure addressing the treatment of serious rare diseases.

Clinical Evidence

Viltolarsen 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]

A phase II study evaluated 2 doses of viltolarsen in 16 ambulatory boys aged 4 to 9 years with a DMD diagnosis and DMD gene amenable to exon 53 skipping over 24 weeks. Ambulatory boys on a stable corticosteroid regimen for at least 3 months who could complete time to stand from supine, time to run/walk 10 m, and time to climb 4 stairs assessments were included. The study was a multicenter, 2 period dose-finding clinical trial. The first study period, which corresponded to the first 4 weeks of treatment following enrollment, was double-blinded and placebo-controlled. Participants in both dose cohorts were randomized 3:1 to receive viltolarsen or placebo. 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. Primary study outcomes included safety, tolerability, and pharmacokinetics of low-dose (40 mg/kg per week) and high-dose (80 mg/kg per week) viltolarsen in ambulant boys with DMD. Efficacy was assessed based on change from baseline in dystrophin protein level (measured as % of the dystrophin level in healthy subjects, i.e., % of normal) at Week 25. Muscle dystrophin production was assessed as protein production by Western blot for the primary study efficacy outcome and as dystrophin mRNA splicing on RT-PCR, dystrophin protein production by MS, and dystrophin localization by IF staining for secondary study efficacy outcomes. Additional secondary efficacy outcomes were gross motor skill assessments of timed function tests, including time to stand from supine, time to run/walk 10 m, time to climb 4 stairs, North Star Ambulatory Assessment, and 6-minute walk test as well as quantitative muscle testing. These outcomes were compared with a matched natural history control group from the Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study (DNHS).

In patients who received viltolarsen 80 mg/kg once weekly, mean dystrophin levels increased from 0.6% of normal at baseline to 5.9% of normal by Week 25, with a mean change in dystrophin of 5.3% of normal levels ($p = 0.01$) as assessed by validated Western blot; 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, mean dystrophin levels increased from 0.6% of normal at baseline to 4.2% of normal by Week 25, with a mean change in dystrophin of 3.7% of normal levels; the median change from baseline was 1.9%.

Comparison of viltolarsen-treated participants with 65 age-matched and treatment matched natural history controls from CINRG DNHS suggested evidence of clinical benefit of viltolarsen treatment. Viltolarsen-treated participants showed improvement or stabilization of function over the 25-week period, whereas the CINRG DNHS external comparator group exhibited a decline in all timed function tests, except for time to climb 4 stairs. Velocity in the time to run/walk 10 m test significantly improved in viltolarsen-treated participants at weeks 13 and 25 compared with a decline in controls from CINRG DNHS (change at 25 weeks compared with baseline: viltolarsen, 0.23 m/s; control, −0.04m/s). The 6-minute walk test showed significant improvement at week 25 in viltolarsen treated participants, whereas results from CINRG DNHS controls declined over the same period (change at 25 weeks compared with baseline: viltolarsen, 28.9 m; control, −65.3 m). Significant improvements in time to stand from supine were observed (change at 25 weeks compared with baseline: viltolarsen, −0.19 s; control, 0.66 s). Velocity in the time to stand from supine test and time to climb 4 stairs test as well as North Star Ambulatory Assessment similarly displayed improvement or stabilization, but the differences between viltolarsen treatment and external comparator controls were not

significant. Measures of muscle strength by isometric testing showed no differences between viltolarsen-treated participants and the CINRG DNHS external comparator control group.[7]

RACER53 is an ongoing 48-week, phase 3 double-blind, placebo controlled, randomized clinical trial that will evaluate the efficacy of viltolarsen in ambulatory DMD patients with out-of-frame deletion mutations amenable to skipping exon 53. The study will enroll 74 boys from 4 to 8 years of age with genotypically confirmed DMD on a stable dose of corticosteroids who can walk independently without assistive devices with a time to stand of less than 10 seconds. The primary endpoint is the change from baseline to Week 48 in the time to stand. Secondary outcomes include the change in time to run/walk 10 meters, change in 6MWT, change in the NSAA, change in time to climb 4 steps, and change in muscle force contraction measured by dyanometry.[8]

The SKIP-NMD trial of golodirsen is a US-based, blinded, placebo-controlled, dose-escalation two-part Phase I/II RCT of male patients aged six to 15 years with a DMD diagnosis and DMD gene amenable to exon 53 skipping. Patients age 6 to 15 years with stable cardiac and pulmonary function, and on a stable dose of corticosteroids for at least six months were included. Additional inclusion criteria included a baseline six-minute walk test (6MWT) of greater than 250m, a North Star Ambulatory Assessment (NSAA) score of greater than 17 or a rise time of less than 7 seconds. In part one, 12 patients were randomized to receive once-weekly intravenous infusions at escalating doses of 4, 10, 20, 30 mg/kg of golodirsen or matching placebo for 12 weeks. Part two consists of an open-label period of all patients from part one and 13 newly recruited patients who are receiving once-weekly infusions of 30 mg/kg of golodirsen for up to 168 weeks.

Part one of the SKIP-NMD trial assessed safety and tolerability. In part two, the primary endpoints are change from baseline in 6MWT at 144 weeks and change in dystrophin protein levels at 48 weeks. Secondary endpoints include drug pharmacokinetics, change from baseline in FVC percent predicted, and change from baseline in dystrophin intensity at 144 weeks.

At the time of pre-planned interim analysis, data from baseline and Week 48 muscle biopsies, exon 53 skipping, and dystrophin localization were available for 25 patients on golodirsen. The study is ongoing, and results for the primary efficacy endpoint of 6MWT at Week 144 are not yet available. Mean baseline of dystrophin in the trial was reported to be 0.095% of normal. At 48 weeks, the mean level of dystrophin had increased to 1.019% of normal resulting in an absolute increase of 0.918% of normal ($p < 0.001$). A clinically meaningful change in level of dystrophin has not yet been established in humans. As such, the clinical significance of these results is not clear. Among individual patients, dystrophin levels at Week 48 ranged from 0.09% to 4.30%.[9-11]

ESSENCE is an ongoing 96-week, Phase 3, double-blind, placebo controlled, randomized clinical trial that will evaluate the efficacy of golodirsen and casimersen in DMD patients with out-of-frame deletion mutations amenable to skipping exon 53 and exon 45, respectively. The study will enroll 222 boys from 7 to 13 years of age with genotypically confirmed DMD and 6MWT ≥ 300 m and ≤ 450 m. The primary endpoint is the change from baseline to Week 96 in 6MWT.[12]

Viltolarsen or golodirsen have not been studied in DMD that is not amenable to exon 53 skipping, nor in other forms of muscular dystrophy (e.g., Becker muscular dystrophy).[1,6]

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Viltepso 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. This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with Viltepso. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

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Policy History/Revision Information

Date	Summary of Changes
08/01/2023	**Coverage Rationale** • Replaced reference to "6-Minute Walk *Time*" with "6-Minute Walk *Test*" **Supporting Information** • Updated *References* section to reflect the most current information • Archived previous policy version 2022D0095E

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.