09-J4000-53

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Subject: Delandistrogene moxeparvovec-rokl (Elevidys)

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DESCRIPTION:

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. This X-linked recessive disorder is caused by mutations (mainly deletions) in the dystrophin gene that lead to an absence or defect in the dystrophin protein.

Dystrophin is thought to maintain the structural integrity of the muscle cell membrane by connecting the cytoskeleton to the underlying extracellular matrix and acting as a scaffold for several molecules that also contribute to normal muscle physiology. Absence of dystrophin leads to mitochondrial dysfunction and damage, with inflammatory processes also appearing to contribute to muscle pathology. Muscle fibers ultimately undergo necrosis with replacement by adipose and connective tissue. Principal disease manifestations include progressive degeneration of skeletal and cardiac muscle, leading to loss of physical function in childhood and adolescence with premature death from respiratory and/or cardiac failure in the second to fourth decade.

As males have only one X chromosome, and thus 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. DMD has an estimated incidence of 1 in 3,500 male births. Available data suggests around 83% of DMD patients have genotypes amenable to exon skipping, and that 13% of DMD patients have genotypes that are amenable to exon 51 skipping.

Treatment options for DMD predominantly focus on management of symptoms and secondary complications. Glucocorticoids are the only pharmacological treatments that have been shown to

improve skeletal muscle strength and function in reproducible randomized controlled trials; they also reduce the risk of scoliosis, stabilize pulmonary function, and may also improve cardiac function. Current guidelines recommend initiation of glucocorticoids (such as prednisolone) once patients reach a plateau of motor skill development, generally at age 4-6 years, but prior to onset of motor decline. 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.

Delandistrogene moxeparvovec-rokl (Elevidys), an adeno-associated virus vector-based gene therapy, was approved by the U.S. Food and Drug Administration (FDA) in June 2023 for the treatment of ambulatory pediatric patients aged 4 through 5 years with DMD with a confirmed mutation in the DMD gene. This indication was approved under accelerated approval based on expression of delandistrogene moxeparvovec-rokl microdystrophin in skeletal muscle observed in patients treated with delandistrogene moxeparvovec-rokl. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Approval of delandistrogene moxeparvovec-rokl was primarily based on data from two clinical trials (Study 1 and Study 2). Study 1 is an ongoing multi-center study including:

- Part 1: a 48-week, randomized, double-blind, placebo-controlled period
- Part 2: a 48-week period that began following completion of Part 1. Patients who received placebo during Part 1 were treated with Elevidys, and patients treated with Elevidys during Part 1 received placebo.

The study population consisted of male ambulatory DMD patients (N=41) aged 4 through 7 years with either a confirmed frameshift mutation, or a premature stop codon mutation between exons 18 to 58 in the DMD gene. Patients were randomized 1:1 to receive either Elevidys (N=20) or placebo (N=21), as a single intravenous infusion via a peripheral limb. Randomization was stratified by age (i.e., aged 4 to 5 years vs. aged 6 to 7 years). In the Elevidys group, eight patients received 1.33 × 1014 vg/kg of Elevidys, and 12 patients received lower doses.

All subjects were on a stable dose of corticosteroids for DMD for at least 12 weeks prior to Elevidys infusion. All randomized subjects had baseline anti-AAVrh74 antibody titers <1:400 as determined by an investigational total binding antibody ELISA. One day prior to treatment with Elevidys or placebo, the subject's background dose of corticosteroid for DMD was increased to at least 1 mg/kg of a corticosteroid (prednisone equivalent) daily and was continued at this level for at least 60 days after the infusion, unless earlier tapering was clinically indicated.

The primary objectives of Study 1 were to evaluate expression of Elevidys micro-dystrophin in skeletal muscle, and to evaluate the effect of Elevidys on the North Star Ambulatory Assessment (NSAA) total score. Results of Elevidys micro-dystrophin measured by western blot are presented in Table 1. The change in NSAA total score was assessed from baseline to Week 48 after infusion of Elevidys or placebo. The difference between the Elevidys and placebo groups was not statistically significant (p=0.37). The least squares (LS) mean changes in NSAA total score from baseline to Week 48 was 1.7 (standard error [SE]: 0.6) points for the Elevidys group and 0.9 (SE: 0.6) points for the placebo group.

Exploratory subgroup analyses showed that for subjects aged 4 through 5 years, the LS mean changes (SE) in NSAA total score from baseline to Week 48 were 4.3 (0.7) points for the Elevidys group, and 1.9 (0.7) points for the placebo group, a numerical advantage for Elevidys. For subjects aged 6 through 7 years, the LS mean changes (SE) in NSAA total score from baseline to Week 48 were -0.2 (0.7) points for the Elevidys group and 0.5 (0.7) points for the placebo group, a numerical disadvantage for Elevidys.

Study 2 is an ongoing, open-label, multi-center study which includes a cohort of 20 ambulatory male DMD subjects aged 4 through 7 years. All 20 subjects have a confirmed frameshift mutation, canonical splice site mutation, or premature stop codon mutation in the DMD gene. At study entry, 75% of subjects were white with a mean age of 5.81 years (range: 4.38 to 7.94), mean weight of 21.2 kg (range: 15.2 to 33.1), mean NSAA total score of 22.1 points (range: 18 to 26), and mean time to rise from floor of 4.2 seconds (range: 2.4 to 8.2). Subjects received corticosteroids for DMD before infusion. All subjects had baseline anti-AAVrh74 antibodies titers <1:400 as determined by the investigational total binding antibody ELISA and received a single intravenous infusion of 1.33 × 1014 vg/kg Elevidys.

The primary objective of the study was to evaluate the effect of Elevidys micro-dystrophin expression as measured by western blot. Results are presented in Table 1.

Table 1: Elevidys Micro-Dystrophin Expression in Studies 1 and 2 (Western Blot Assay)[abcd]

Western blot (% of Elevidys micro-dystrophin compared to control)	Study 1 (Week 12) Part 1 (n = 6)	Study 1 (Week 12) Part 2 (n=21)	Study 2 (Week 12) Cohort 1 (n = 20)
Mean change from baseline (SD)	43.4 (48.6)	40.7 (32.3)	54.2 (42.6)
Median change from baseline (Min, Max)	24.3 (1.6, 116.3)	40.8 (0.0, 92.0)	50.6 (4.8, 153.9)

a. All patients received 1.33 x 1014 vg/kg, as measured by ddPCR

b. Muscle biopsies were obtained from the gastrocnemius

c. Change from baseline was statistically significant

d. Adjusted for muscle content. Control was level of wild-type (normal) dystrophin in normal muscle.

For subjects aged 4 through 5 years who received 1.33 × 1014 vg/kg of Elevidys, the mean (SD) Elevidys micro-dystrophin expression levels (change from baseline) at Week 12 following Elevidys infusion were 95.7% (N=3, SD: 17.9%) in Study 1 Parts 1 and 2 and 51.7% (N=11, SD: 41.0%) in Study 2 Cohort 1.

Assessment of Elevidys micro-dystrophin levels can be meaningfully influenced by differences in sample processing, analytical technique, reference materials, and quantitation methodologies. Therefore, valid comparisons of Elevidys micro-dystrophin measurements obtained from different assays cannot be made.

POSITION STATEMENT:

Delandistrogene moxeparvovec-rokl (Elevidys) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member is diagnosed with Duchenne muscular dystrophy (DMD)
2. Member has a confirmed mutation in the DMD gene **AND** does not have any deletion in exon 8 and/or exon 9 – laboratory documentation must be submitted
3. Member is ambulatory and not wheelchair dependent – documentation from the medical record must be submitted
4. At the time of the infusion, member is 4 through 5 years old
5. Member has anti-AAVrh74 total binding antibody titers <1:400 – laboratory documentation must be provided
6. Dose does not exceed 1.33×10^{14} vg/kg
7. Treatment is prescribed by a specialist in DMD
8. At the time of infusion, member is not enrolled in a clinical trial to receive an experimental drug or gene therapy for DMD
9. Member has **NOT** previously received gene therapy for treatment of DMD

Approval duration: 6 months or until the member's 6th birthday (whichever occurs first) to allow for one-time infusion of therapy (1 lifetime treatment)

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Select patients for treatment with anti-AAVrh74 total binding antibody titers <1:400
- Recommended dosage: 1.33 ×1014 vector genomes (vg) per kg of body weight
- One day prior to infusion, initiate a corticosteroid regimen for a minimum of 60 days. Recommend modifying corticosteroid dose for patients with liver function abnormalities
- Administer as an intravenous infusion over 1-2 hours. Infuse at a rate of less than 10 mL/kg/hour

Dose Adjustments

- None

Drug Availability

- Suspension for intravenous infusion with a nominal concentration of 1.33 × 1013 vg/mL

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- Patients with any deletion in exon 8 and/or exon 9 in the DMD gene

Precautions/Warnings

- Acute serious liver injury
- Immune-mediated myositis
- Myocarditis
- Pre-existing immunity against AAVrh74

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J1413	Injection, delandistrogene moxeparvovec-rokl, per therapeutic dose

ICD-10 Diagnosis Codes That Support Medical Necessity

G71.01	Duchenne or Becker muscular dystrophy

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

North Start Ambulatory Assessment (NSAA): validated rating scale used to measure the impact of Duchenne muscular dystrophy on ambulatory performance. (https://www.touchneurology.com/wp-content/uploads/sites/3/2018/03/www.musculardystrophyuk.org_assets_0000_6388_NorthStar.pdf)

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 05/08/24.

GUIDELINE UPDATE INFORMATION:

06/15/24	New Medical Coverage Guideline.
07/15/24	Revision to position statement to clarify approval duration, added HCPCS code.