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Subject: Eteplirsen (Exondys 51)

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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.

Eteplirsen was approved by the U.S. Food and Drug Administration (FDA) in September 2016 for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. This indication was approved under accelerated approval using a surrogate endpoint: increase in dystrophin in skeletal muscle observed in some patients. The FDA label includes the following statement, “A clinical benefit of EXONDYS 51 has not been established. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.” Prior to FDA approval, the Peripheral and Central Nervous System Drugs Advisory Committee of the FDA held a meeting and voted against approval of Eteplirsen as treatment for DMD. Much uncertainty exists regarding whether the small observed increase in dystrophin will confer a clinically meaningful benefit.

Eteplirsen is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) class that selectively binds to exon 51 of the dystrophin pre-messenger ribonucleic acid (pre-mRNA). This causes the exon to be skipped and prevents that part of the code from being read during mRNA processing, thereby repairing the mutated reading frame in the mRNA coding sequence in patients with a deletion in exons 45-50, 47-50, 48-50, 49-50, 50, 52, or 52-63 of this gene. In doing so, eteplirsen enables the production of an internally truncated, yet functional, dystrophin protein.

Eteplirsen was evaluated in several clinical studies in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. Study 201 was a single-center, double-blind, placebo-controlled study in 12 patients with DMD. Patients were randomized (1:1:1) to eteplirsen 30 mg/kg/week, eteplirsen 50 mg/kg/week, or placebo (4 patients per group). After 24 weeks, the 4 patients originally randomized to placebo were re-randomized to eteplirsen 30 mg/kg/week (n=2) or eteplirsen 50 mg/kg/week (n=2). The trial was eventually extended to an open-label phase (Study 202) where all patients received eteplirsen, although investigators and patients remained blinded to dose. These patients have continued to receive eteplirsen for more than 4 years. This continuous study is referred to as Study 201/202.

In Study 201, patients were randomized to receive weekly infusions of eteplirsen (30 mg/kg, n=4); eteplirsen (50 mg/kg, n=4), or placebo (n=4) for 24 weeks. The primary endpoint was dystrophin production; a clinical outcome measure, the 6-minute walk test (6MWT), was also assessed. The 6MWT measures the distance that a patient can walk on a flat, hard surface in a period of 6 minutes. Patients had a mean age of 9.4 years, a mean 6-minute walk distance (6MWD) at baseline of 363 meters, and were on a stable dose of corticosteroids for at least 6 months. There was no significant difference in change in 6MWD between patients treated with eteplirsen and those treated with placebo.

Patients who participated in Study 201/202 were compared to an external control group. The primary clinical efficacy outcome measure was the 6MWT. Eleven patients in Study 201/202 had a muscle biopsy after 180 weeks of treatment with eteplirsen, which was analyzed for dystrophin protein level by Western blot. Study 201/202 failed to provide evidence of a clinical benefit of eteplirsen compared to the external control group. The average dystrophin protein level after 180 weeks of treatment with eteplirsen was 0.93% of the dystrophin level in healthy subjects. Baseline measurements were not available.

Study 301 is an externally controlled study where all patients are receiving open-label eteplirsen, 30 mg/kg, by weekly infusion. The study is ongoing and still accruing patients. Interim data were obtained from patients in this study and the FDA's approval was based on the unpublished results of Study 301.

In Study 301, 13 patients were treated with open-label eteplirsen (30 mg/kg) weekly for 48 weeks and had a muscle biopsy at baseline and after 48 weeks of treatment. Patients had a mean age of 8.9 years and were on a stable dose of corticosteroids for at least 6 months. Dystrophin levels in muscle tissue were assessed by Western blot. In the 12 patients with evaluable results, the pre-treatment dystrophin level was 0.16% ± 0.12% (mean ± standard deviation) of the dystrophin level in a healthy subject and 0.44% ± 0.43% after 48 weeks of treatment with eteplirsen ($p < 0.05$). The median increase after 48 weeks was 0.1%. It should be noted that the clinical significance of this is unknown.

Individual patient dystrophin levels from Study 301 are shown in Table 1.

Table 1. Western Blot Results: eteplirsen -Treated (Week 48) vs Pre-treatment Baseline (% Normal Dystrophin) (Study 301)

Patient Number	Baseline % normal dystrophin	Week 48 % normal dystrophin	Change from Baseline % normal dystrophin
1	0.13	0.26	0.13
2	0.35	0.36	0.01
3	0.06	0.37	0.31
4	0.04	0.10	0.06
5	0.17	1.02	0.85
6	0.37	0.30	-0.07
7	0.17	0.42	0.25
8	0.24	1.57	1.33
9	0.11	0.12	0.01
10	0.05	0.47	0.43
11	0.02	0.09	0.07
12	0.18	0.21	0.03
Mean	0.16	0.44	0.28; p=0.008

In the 88 patients who received ≥30 mg/kg/week of eteplirsen for up to 208 weeks in clinical studies, the following events were reported in ≥10% of patients and occurred more frequently than on the same dose in Study 201: vomiting, contusion, excoriation, arthralgia, rash, catheter site pain, and upper respiratory tract infection. There have been reports of transient erythema, facial flushing, and elevated temperature occurring on days of eteplirsen infusion.

There is an ongoing Phase III confirmatory trial evaluating the efficacy of eteplirsen in DMD with a target enrollment of 160 patients. The estimated completion date is January 2019.

POSITION STATEMENT:

Initiation of eteplirsen (Exondys 51) **meets the definition of medical necessity** when all of the following criteria are met:

1. Indication for use is treatment of Duchenne muscular dystrophy (DMD)

2. Member has a mutation of the DMD gene amenable to exon 51 skipping – laboratory documentation must be provided
3. Member is ambulatory (e.g., able to walk with assistance, not wheelchair dependent) – documentation from the medical record must be provided
4. Member has a recent (within four weeks of request) pre-treatment 6-Minute Walk Time of at least 300 meters while walking independently (e.g., without assist, cane, walker, wheelchair) – documentation from the medical record must be provided
5. Treatment is prescribed by a board certified (or board eligible) neurologist
6. Member is not concurrently enrolled in a clinical trial to receive an experimental therapy for DMD
7. Dose does not exceed 30 mg/kg once weekly

Approval duration: 3 months

Continuation of eteplirsen (Exondys 51) **meets the definition of medical necessity** when all of the following criteria are met:

1. Authorization/reauthorization has been previously approved by Florida Blue in the past two years for treatment of Duchenne muscular dystrophy (DMD), OR the member has previously met all indication-specific initiation criteria
2. Member has a mutation of the DMD gene amenable to exon 51 skipping – laboratory documentation must be provided
3. Member has demonstrated a beneficial response in DMD-associated symptoms – documentation from medical record must be provided
4. Member is ambulatory (e.g., able to walk with assistance, not wheelchair dependent) – documentation from the medical record must be provided
5. Member has a recent (within four weeks of request) 6-Minute Walk Time of at least 300 meters while walking independently (e.g., without assist, cane, walker, wheelchair) – documentation from the medical record must be provided
6. Treatment is prescribed by a board certified (or board eligible) neurologist
7. Member is not concurrently enrolled in a clinical trial to receive an experimental therapy for DMD
8. Dose does not exceed 30 mg/kg once weekly

Approval duration: 6 months

DOSAGE/ADMINISTRATION:

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FDA-approved

- 30 milligrams per kilogram of body weight once weekly
- Administer as an intravenous infusion over 35 to 60 minutes

Dose Adjustments

- None

Drug Availability

- 100 mg/2 mL (50 mg/mL) in single-dose vial
- 500 mg/10 mL (50 mg/mL) in single-dose vial

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- None

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J1428	Injection, eteplirsen, 10 mg

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 revised date.

DEFINITIONS:

6 minute walk test: assesses distance walked over 6 minutes as a sub-maximal test of aerobic capacity/endurance

9 Hole Peg Test: a brief, standardized quantitative test of upper extremity function

Maximum Voluntary Isometric Contraction Test: assesses muscle strength

North Star Ambulatory Assessment: a functional scale designed for ambulant boys affected by DMD

RELATED GUIDELINES:

None

OTHER:

None

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 12/11/19.

GUIDELINE UPDATE INFORMATION:

10/15/16	New Medical Coverage Guideline.
04/01/17	Revision to guideline consisting of adding HCPCS code C9484.
12/15/17	Review and revision to guideline, consisting of updating references.
01/01/18	Annual HCPCS coding update: added HCPCS code J1428 and removed code C9484.
01/15/19	Review and revision to guideline, consisting of updating references.
1/15/20	Review and revision to guideline, consisting of updating position statement, coding, and references.