Kansas City

An Independent Licensee of the Blue Cross and Blue Shield Association

Exondys 51 (eteplirsen) injection

Policy Number: 5.01.618 **Last Review:** 10/2018
Origination: 10/2016 **Next Review:** 10/2019

Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for Exondys 51 (eteplirsen). This is considered investigational.

When Policy Topic is covered

Not Applicable

When Policy Topic is not covered

The use of eteplirsen is considered **investigational** for all indications, including but not limited to the treatment of Duchenne muscular dystrophy

Considerations

N/A

Description of Procedure or Service

EXONDYS 51 is an antisense oligonucleotide 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 51 skipping. Eteplirsen induces skipping of exon 51 which allows for the creation of shorter-than-normal, but partially functional, dystrophin - the muscle protein missing in those diagnosed with DMD **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. [1]

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

Injection:

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

Rationale

On September 19, 2016, the Food and Drug Administration (FDA) approved eteplirsen (Exondys 51) for the treatment of individuals who have a confirmed mutation of the dystrophin gene that is amenable to exon 51 skipping (Product Information [PI] Label, 2016). Eteplirsen, which has orphan drug status, was under priority review. Priority review designation is given to drugs that offer major advances in treatment, or provide a treatment where no adequate therapy exists. Eteplirsen was also granted accelerated approval, which allows a surrogate endpoint to be used for serious diseases in which there exists an unmet need for therapy. In April of 2016, 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 (FDA, 2016b). Ultimately, eteplirsen secured the FDA's approval based on an increase in dystrophin seen in the skeletal muscle of some boys treated with the drug; however, uncertainty exists regarding whether the small observed increase in dystrophin will confer a clinically meaningful benefit.

The FDA labeled indications include a statement that a clinical benefit has not been established and continued approval is contingent upon verification of a clinical benefit in ongoing confirmatory clinical trials (PI Label, 2016).

Mendell and colleagues (2013) conducted a double-blind, placebo-controlled study to evaluate eteplirsen's ability to induce dystrophin production and improve distance walked on the 6-minute walk test (6MWT). Boys diagnosed with DMD (n=12), aged 7 to 13 years, with confirmed deletions correctable by skipping exon 51, and a stable steroid regimen, were randomized to weekly intravenous (IV) infusions of 30 or 50 mg/kg of eteplirsen or placebo for 24 weeks (n=4 per group). The placebo group switched to 30 or 50 mg/kg eteplirsen (n=2 per group) at week 25 and treatment became open-label thereafter. All study enrollees had muscle biopsies at baseline and week 48. Efficacy measurements included dystrophin-positive fibers from biopsy and distance walked on the 6MWT. At week 24, the 30 mg/kg eteplirsen group's percentage of dystrophin-positive fibers had increased to 23% of normal, whereas no increases were found in the placebo group ($p \leq 0.002$). Of the 4 boys who had consistent increases in dystrophin-positive fibers, 2 (50%) concurrently experienced a rapidly progressive decline in motor function (ability to ambulate was lost), casting considerable doubt on the plausibility of dystrophin-positive fibers' reliability as a surrogate endpoint for clinically meaningful benefit. The increases in the treatment group's dystrophin-positive fibers were even greater by week 48 (52% and 43% in the 30 and 50 mg/kg cohorts, respectively). Boys from the treatment group with evaluable ambulation experienced a 67.3 m benefit compared to the placebo group ($p \leq 0.001$); however, this benefit includes 4 boys treated with the non FDA-approved dose of 50 mg/kg dose, and only 2 who were treated with the 30 mg/kg dose. No severe adverse events were reported. The FDA has recommended retraction of this study due to concerns related to interpretation of its findings.

In 2016, an open-label extension study was conducted by Mendell and colleagues to evaluate the long-term efficacy and safety of eteplirsen. Study enrollees received 30mg/kg (n=6) or 50mg/kg (n=6) of IV eteplirsen. At 36 months of follow-up, a total of 12 individuals had been enrolled and treated with eteplirsen. Only subjects treated with corticosteroids were included in the analysis due to its previously demonstrated efficacy on slowing disease progression. Although at 12 months there was no difference between eteplirsen and historical controls on 6MWT scores, at 3 years the eteplirsen cohort was found to have a 151 m advantage in the 6MWT over the matched historical controls identified from two natural history studies (n=13; $p<0.01$). Also at the 3-year follow-up, 16.7% of the treatment cohort (n=2/12) had lost the ability to ambulate while 46.2% of the historical controls had lost ambulation (n=6/13). Despite the authors' conclusions, the FDA stated,

> There are significant concerns regarding the ability to draw valid conclusions from this historically controlled comparison. Moreover, comparisons between patients in Study 201/202 [Mendell 2013 and 2016] and patients in a related development program who had received placebo suggest that the change in 6-minute walk distance with eteplirsen was consistent with the natural history of the disease.

A direct comparison of change in pulmonary function was also not possible due to a lack of data from the historical controls. At study end, the average dystrophin protein levels were 0.93% of the dystrophin level in healthy subjects; baseline measurements were not available. Over the course of the 3-year study, there were no serious events reported and no reports of systemic reactions. There were no reported infusion interruptions or dose adjustments.

Overall, both Mendell studies (2013 and 2016) failed to meet their primary endpoints of a significant improvement in 6MWT scores, and methodological study limitations hinder the ability to interpret the efficacy of etiplersen as a disease modifying therapy for DMD. Furthermore, expert consensus suggests that 6MWT is not the best reflection of function in individuals with DMD. The North Star Ambulatory Assessment (NSAA) provides a more comprehensive outcome measure and was specifically designed to measure the functional ability of ambulatory individuals with DMD (Ricotti, 2016). The NSAA scores for eteplirsen-treated boys in both studies had marked declines over the course of the study (FDA, 2016a).

The FDA's final approval was based on an unpublished, open-label study of 13 boys who were on a stable dose of corticosteroids (≥ 6 months) and who were treated with eteplirsen (30mg/kg) weekly for 48 weeks (1 subject was unavailable for analysis at 48 weeks). Muscle biopsies were obtained at both baseline and study-end to assess the study's primary endpoint of dystrophin levels in muscle tissues. The average age was 8.9 years at enrollment. Baseline dystrophin levels in study participants averaged 0.16% (± 0.12%) of the dystrophin level in a healthy subject and at study-end, had a statistically significant increase (p=0.008), resulting in an average of 0.44% (± 0.43%) the level in a healthy subject. Overall, there was a median increase after 48 weeks of 0.1% in the dystrophin levels after treatment with eteplirsen. A statistically significant increase in dystrophin was reported (0.22% to 0.32% of normal). However, a statistically significant, yet minimal magnitude, increase in dystrophin, the surrogate endpoint of this study, does not assure a clinical benefit. Eteplirsen's accelerated approval was based on the surrogate endpoint of the drug's demonstrated ability to increase dystrophin levels in the muscle tissues of subjects treated; however, experts in the field have stated that "induction of approximately 10% of normal dystrophin levels sets a minimum level to confer measurable clinical benefit," in reference to Becker's Muscular Dystrophy (BMD) (a very similar, but less severe form of muscular dystrophy). Furthermore, the trial's internal validity was compromised by the use of differing methods of evaluating dystrophin levels (Western blot [percent of normal] and immunofluorescence [percent positive fibers]), variable time points of specimen collection, and from variable muscles. Given that independent methods were used to quantify dystrophin levels, a correlation within individuals was conducted and the correlation was found to be weak. The aforementioned multitude of limitations cast further doubt on the reliability of dystrophin levels as a surrogate endpoint for clinical efficacy in DMD (FDA, 2016). Continued FDA approval is contingent upon the drug's ability to successfully demonstrate a clinically meaningful benefit. The most frequently reported adverse events (≥ 35%) across clinical trials, when compared to control groups, were balance disorder and vomiting (FDA PI Label, 2016).

There is an on-going Phase III confirmatory study on eteplirsen's efficacy as a treatment for DMD with a target enrollment of 160 subjects (PROMOVI; NCT02255552). PROMVI is an open-label, multi-center 48-week study. Boys with DMD that are amenable to skipping exon 51 will be administered 30 mg/kg of eteplirsen IV, weekly. Boys with DMD not amenable to skipping exon 51 will serve as a concurrent control arm. Eligibility criteria are similar to the preceding studies conducted investigating the safety and efficacy of eteplirsen and include boys aged 7 to 16 years of age on a stable dose of corticosteroids. The primary outcome of interest is change in 6MWT from baseline and secondary study objectives include documented changes from baseline in the percent of dystrophin-positive muscle fibers and PFT results. The estimated primary completion date is January 2019. There are additional studies being conducted to assess eteplirsen's efficacy in both early (ages 4-6) and more advanced (ages 7-21) stages of DMD (NCT02286947, NCT02420379).

In summary, the clinical benefit of treatment for DMD with eteplirsen, including improved motor function, has not been demonstrated. Establishment of a clinical benefit is warranted in on-going clinical trials.

Other Oligonucleotide Drugs

The FDA granted priority review status to another antisense oligonucleotide (PRO051 or drisapersen) which was very similar in composition to eteplirsen. The safety and efficacy of drisapersen was evaluated by Voit and colleagues (2014) in a phase II double-blind, placebo-controlled study. Study enrollees (n=53) were boys at least 5 years in age, with DMD, a confirmed drisapersen-correctable mutation, and stable steroid regimen. The primary study outcome was a 6MWT following continuous treatment for 25 weeks. At 25 weeks the mean distance covered by the continuously treated group increased by 31.5 m from baseline. However, by week 49 the difference between treated and placebo cohorts was no longer statistically significant. Drisapersen was ultimately not approved by the FDA; research and development of the drug has since been discontinued by the manufacturer.

BACKGROUND

Duchenne Muscular Dystrophy

Muscular dystrophy (MD) refers to a diverse group of genetic diseases (disorders) characterized by a decrease in muscle mass over time, including progressive damage and weakness of facial, limb, breathing, and heart muscles. Some disorders within this group, referred to as dystrophinopathies, are categorized based on clinical features (such as, the age when signs are first seen), genetic (inheritance) pattern, the muscles affected, and muscle biopsy features. A major type of MD is DMD, and is the most common form affecting children.

DMD is X-linked recessive and penetrance is complete in males. The gene that codes for dystrophin is the largest known human gene. A molecular confirmation of DMD is achieved by confirming the presence of a pathogenic variant in this gene by a number of available assays. The large size of the dystrophin gene results in a complex mutational spectrum with over 5000 different reported mutations as well as a high spontaneous mutation rate. The DMD gene is the only gene in which mutations are known to cause DMD and DMD-associated cardiomyopathy.

It is estimated that 9000-12,000 boys in the United States (US) have been diagnosed with DMD. The disease prevalence for DMD is typically estimated with the prevalence of BMD. Diagnosis usually occurs around age 6 when symptoms begin to manifest and by the age of 10 most boys have lost the ability to ambulate. Few individuals survive into their 4th decade of life. The current standard of care focuses on management of symptoms associated with DMD and includes treatment with steroids to reduce the characteristic loss in muscle function.

Eteplirsen targets exon 51 using a molecule called an antisense oligonucleotide. It has been estimated that 13% of boys with DMD may benefit from skipping exon 51 (1200-1500 boys in the US). DMD is caused by a mutation in the gene encoding the protein dystrophin. Eteplirsen induces skipping of exon 51 in the dystrophin pre-messenger RNA to correct this DMD-related mutation. By restoring the messenger RNA reading frame, a truncated but partially functional form of the dystrophin protein can be produced by muscle cells; similar truncated dystrophin is found in a less severe form of muscular dystrophy, BMD.

Most common adverse reactions listed on the FDA PI Label (2016) include the following:

- The following events were reported in ≥10% of those who received Exondys 51: vomiting, contusion, excoriation, arthralgia, rash, catheter site pain, and upper respiratory tract infection.
- Exondys 51 has been reportedly associated with transient erythema, facial flushing and elevated temperature.

Additional considerations and recommendations from the FDA PI Label (2016):

- There is no geriatric experience in Exondys 51.
- 100% of study participants were male, thus the safety and efficacy of Exondys 51 in females is unknown.
- 89% of study participants who received Exondys 51 were Caucasian, thus the potential impact of race on safety and efficacy of this drug is unknown.
- Exondys 51 has not been studied in individuals with renal or hepatic impairment.
- All subjects in clinical trials were on a stable dose of corticosteroids for at least 6 months prior to initiating therapy with Exondys 51.

DEFINITIONS:
Antisense oligonucleotide: a short strand of deoxyribonucleotide analogue that hybridizes with the complementary messenger ribonucleic acid in a sequence-specific manner via Watson-Crick base pairing.

Cardiomyopathy: a condition in which the heart muscle becomes enlarged, thick, or rigid. In rare cases, the muscle tissue in the heart is replaced with scar tissue.

Exon: Parts of a gene sequence that are expressed in a protein.
Pulmonary function tests: A set of non-invasive tests that show how well the lungs are working by measuring lung volume, capacity, rates of flow, and gas exchange.

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Billing Coding/Physician Documentation Information

This is a medical benefit; limited distribution network

J3490 Unclassified drugs [when specified as eteplirsen]

C9484 **Exondys** 51 100 MG/2ML SOLN C9484 Injection, eteplirsen, 10 mg (For Hospital OPPS billing prior to 4/1/17 use C9399) -see also J3490

J1428 **Exondys** 51 500 MG/10ML SOLN J1428 Injection, eteplirsen, 10 mg (Code becomes effective for Medicare billing 1/1/18)

ICD10 G71.0 Muscular Dystrophy

Additional Policy Key Words

5.01.618; BCBSA policy 5.01.27

Policy Implementation/Update Information

10/2016	New policy titled Exondys 51 (eteplirsen) injection
10/2017	Annual review; no changes to policy statement; included reference to BCBSA policy 5.01.27. The local policy was developed prior to the association policy. Statements are the same.
12/2017	Added C9484 and J1428
10/2018	Policy reviewed, no changes made