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OVERVIEW

Duchenne muscular dystrophy is an inherited disorder that results in progressive muscle weakness and loss of muscle mass, primarily affecting males. Duchenne muscular dystrophy is caused by variant(s) in the exon gene responsible for producing dystrophin, a cohesive protein essential for maintaining muscle support and strength. The variant(s) disrupts the translational reading of messenger RNA resulting in an unstable, nonfunctional dystrophin molecule. Eteplirsen and golodirsen are antisense oligonucleotides that induce skipping of exons 51 and 53 respectively and thereby repairing the mutated reading frame. As a result, eteplirsen and golodirsen enable production of an internally truncated, yet functional, dystrophin protein.

MEDICAL CRITERIA

Not applicable.

PRIOR AUTHORIZATION

Not applicable.

POLICY STATEMENT

BlueCHiP for Medicare and Commercial Products

The use of eteplirsen or golodirsen are not covered for all indications including treatment of Duchenne muscular dystrophy as the evidence is insufficient to determine the effects of the technology on health outcomes.

COVERAGE

Benefits may vary between groups/contracts. Please refer to the appropriate Evidence of Coverage for applicable physician administered drug infusion coverage/benefits.

BACKGROUND

Duchenne muscular dystrophy is an X-linked, recessive disorder that occurs in approximately 1 in every 3500 to 5000 males. It primarily affects males. However, a small number of girls are also affected, but they are usually asymptomatic, and even when symptomatic, only present with a mild form of the disease. According to U.S. epidemiologic data, the first signs or symptoms of Duchenne muscular dystrophy are noted at a mean age of 2.5 years (range, 0.2-1 years), and the mean age at definitive diagnosis is 4.9 years (range, 0.3-8.8 years).² Symptoms include motor difficulties such as running, jumping, walking up stairs, and an unusual waddling gait. Some improvement in symptoms may be seen from 3 to 6 years of age, though gradual deterioration resumes and most patients lose ambulation by age 12 and require noninvasive ventilation by late teenage years. Patients progress from needing noninvasive ventilation only during night sleeping, followed by noninvasive ventilation during day and night sleeping, and then noninvasive ventilation during day and night over the course of 5 to 10 years.

Duchenne muscular dystrophy occurs as a result of variant(s) in the gene responsible for producing dystrophin, a cohesive protein that is essential for maintaining muscle support and strength. Duchenne muscular dystrophy is the longest known human gene, and several variants can cause Duchenne muscular dystrophy. Most deletion variants disrupt the translational reading frame in the dystrophin messenger RNA resulting in an unstable, nonfunctional dystrophin molecule. As a result, there is progressive muscle

degeneration leading to loss of independent ambulation, as well as other complications, including respiratory and cardiac complications.³ Genetic testing is required to determine the specific Duchenne muscular dystrophy gene variant(s) for a definitive diagnosis, even when the absence of dystrophin protein expression has been confirmed by muscle biopsy. There are over 4700 variants in the Leiden Duchenne muscular dystrophy mutation database, and the most common variants are concentrated between exons 45 and 53.

The current standard of pharmacotherapy for DMD is corticosteroids for all patients regardless of genetic variant. Treatment is initiated once patients reach a plateau of motor skill development, generally at ages 4 to 6 years, but prior to onset of motor decline. The goal of corticosteroid therapy is to preserve ambulation and minimize respiratory, cardiac, and orthopedic complications. In addition, muscle weakness and pain, cardiac, pulmonary, orthopedic, and endocrine symptoms should be managed.

Regulatory Status

Eteplirsen

In September 2016, eteplirsen (Exondys 51™; Sarepta Therapeutics) was approved by the U.S. Food and Drug Administration (FDA) after orphan drug designation for Duchenne muscular dystrophy patients who have a confirmed variant of the Duchenne muscular dystrophy gene that is amenable to exon 51 skipping. This indication was approved with a fast track designation based on an increase in dystrophin in skeletal muscle observed in some patients treated with eteplirsen.

The FDA, under the accelerated approval regulations (21 CFR 314.510), requires that Sarepta conduct a confirmatory trial to demonstrate the clinical benefit of eteplirsen. In the preceding 3 years after the FDA approval, there has still been no publication of a trial confirming or refuting a clinical benefit of eteplirsen. The European Medicines Agency rejected marketing approval for eteplirsen in September 2018.

For individuals with a confirmed variant of the Duchenne muscular dystrophy gene that is amenable to exon 51 skipping who receive eteplirsen, the evidence includes 1 randomized controlled trial (RCT), 1 ongoing prospective open-label trial with a concurrent untreated control arm and multiple post-hoc studies with historical control. Relevant outcomes are disease-specific survival, change in disease status, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. For the single pivotal RCT, no formal sample size calculations were conducted. A sample size of 12 total patients was selected with 4 patients in 3 treatment groups. There was no statistically significant difference either in the mean change from baseline in the 6-minute walk test distance or change in the North Star Ambulatory Assessment total score between eteplirsen treated patients and placebo-treated patients at week 48. While eteplirsen treatment resulted in dystrophin detection in muscle biopsies suggesting the production of (truncated) dystrophin, the amount of protein produced was very limited according to the Western blot results (0.44% of normal dystrophin at week 48 [Study 301]; 0.93% at week 180 [Study 201/202]). There are no satisfactory data, clearly establishing the effectiveness of the truncated dystrophin. Further, the minimum beneficial amount of dystrophin expression to be translated into a clinical benefit has yet to be established. In the absence of clinical data convincingly demonstrating a clinical effect, it cannot be concluded that the amount of dystrophin expressed with eteplirsen will translate into a clinical benefit to patients. Multiple analysis of long-term follow-up data from study 201/202 and 301 on functional outcome measures such as 6-minute walk test and pulmonary function suggest that the rate of decline in eteplirsen treated patients was less as compared to historical controls. However, the post-hoc nature of the analysis and the fact that the cohorts were retrospectively identified within the untreated group of patients is of serious concern (potential selection bias) and undermines the robustness of the data. Particularly, the 6-minute walk test is subject to inter- and intra-subject variability and is influenced by training and motivation making it a less suitable outcome measure for external control group comparison. Thus the clinical benefit of treating Duchenne muscular dystrophy with eteplirsen, including improved motor function and pulmonary function, has not been demonstrated. A confirmatory, prospective and adequately powered trial is necessary to assess the net health benefit of eteplirsen in patients with Duchenne muscular dystrophy amenable to 51 skipping. The evidence is insufficient to determine the effects of the technology on health outcomes.

Golodirsen

In December 2019, golodirsen (Vyondys 53™; Sarepta Therapeutics) was approved by the FDA after orphan drug designation for Duchenne muscular dystrophy patients who have a confirmed variant of the Duchenne muscular dystrophy gene that is amenable to exon 53 skipping. This indication was approved with a fast track designation based on an increase in dystrophin in skeletal muscle observed in some patients treated with golodirsen.

The FDA, under the accelerated approval regulations (21 CFR 314.510), requires that Sarepta conduct a randomized double-blind, placebo-controlled trial of 96 weeks with an open-label extension to 144 weeks to verify the clinical benefit of golodirsen with the primary endpoint of 6-minute walk test. The expected date of trial completion is April 2024 and final report submission to the FDA by October 2024.

For individuals with a confirmed variant of the Duchenne muscular dystrophy gene that is amenable to exon 53 skipping who receive golodirsen, the evidence includes a 2-part multicenter study which consists of a part 1 randomized, double-blind safety and tolerability study and a part 2 open-label efficacy and safety study. Relevant outcomes are disease-specific survival, change in disease status, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. Results of interim analysis were based on 25 patients who received a weekly intravenous infusion of golodirsen 30 mg/kg. At week 48, the mean change in dystrophin protein levels was 0.924% increase from the baseline (1.019% vs. 0.095%; P <0.001). There are no satisfactory data, clearly establishing the effectiveness of the truncated dystrophin. Further, the minimum beneficial amount of dystrophin expression to be translated into a clinical benefit has yet to be established. In the absence of clinical data convincingly demonstrating a clinical effect, it cannot be concluded that the amount of dystrophin expressed with golodirsen will translate into a clinical benefit to patients. A confirmatory, prospective and adequately powered trial is necessary to assess the net health benefit of eteplirsen in patients with Duchenne muscular dystrophy amenable to 51 skipping. The evidence is insufficient to determine the effects of the technology on health outcomes.

CODING

BlueCHiP for Medicare and Commercial Products

The following HCPCS codes are not covered:

J1428 Injection, eteplirsen, 10 mg

J1429 Injection, golodirsen, 10 mg

RELATED POLICIES

Not applicable.

PUBLISHED

Provider Update, October 2020

Provider Update, July 2019

Provider Update, June 2018

Provider Update, June 2017

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