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Exondys 51™

Policy Number: HS-292

Original Effective Date: 7/6/2017

Revised Date(s): 8/24/2018

APPLICATION STATEMENT

The application of the Clinical Coverage Guideline is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations and state-specific Medicaid mandates, if any.

DISCLAIMER

The Clinical Coverage Guideline (CCG) is intended to supplement certain standard WellCare benefit plans and aid in administering benefits. Federal and state law, contract language, etc. take precedence over the CCG (e.g., Centers for Medicare and Medicaid Services [CMS] National Coverage Determinations [NCDs], Local Coverage Determinations [LCDs] or other published documents). The terms of a member's particular Benefit Plan, Evidence of Coverage, Certificate of Coverage, etc., may differ significantly from this Coverage Position. For example, a member's benefit plan may contain specific exclusions related to the topic addressed in this CCG. Additionally, CCGs relate exclusively to the administration of health benefit plans and are NOT recommendations for treatment, nor should they be used as treatment guidelines. Providers are responsible for the treatment and recommendations provided to the member. The application of the CCG is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations, and any state-specific Medicaid mandates. Links are current at time of approval by the Medical Policy Committee (MPC) and are subject to change. Lines of business are also subject to change without notice and are noted on www.wellcare.com. Guidelines are also available on the site by selecting the Provider tab, then "Tools" and "Clinical Guidelines".

BACKGROUND

The FDA describes Duchenne muscular dystrophy (DMD) as a rare genetic disorder characterized by progressive muscle deterioration and weakness. DMD is the most common type of muscular dystrophy and is caused by an absence of dystrophin, a protein that helps keep muscle cells intact. The disease is progressive and the first symptoms are usually seen between three and five years of age.¹

The disease often occurs in people without a known family history of the condition and primarily affects boys, occurring in about one out of every 3,600 male infants worldwide. In rare cases it can also affect girls.¹ DMD occurs in all ethnic groups.² Although there are a number of different types of muscular dystrophy, Duchenne muscular dystrophy is associated with the most severe clinical symptoms.³

Genetics - Duchenne muscular dystrophy is caused by mutations on one of the X chromosomes carried by the female parent. This gene is responsible for producing a protein called dystrophin, which normally functions to protect muscle fibers. Without dystrophin, muscles are broken down by enzymes, which causes degeneration and

weakness. Females who inherit their mother's defective X chromosome are called carrier females and are usually disease free, although mild symptoms can occur occasionally.²

Signs and Symptoms - Symptoms typically begin to appear in children between the ages of two and three years but may develop earlier or later. Children affected tend to have slower than normal growth in the first few years of life. Frequently, children with DMD will have some degree of cognitive impairment or developmental delay.^{2,4}

Weakness starts in the trunk, and then spreads to extremities, legs are affected before the arms. The child may display trouble running and jumping or going up steps and may use their hands to help push themselves upright from a squatting position or lying down. The child may walk with an unusual or waddling gait. Lumbar lordosis and calf enlargement are usually observed as well as shortening of the Achilles tendons and hyporeflexia or areflexia. Complaints of leg pain may be found with early disease and children are usually wheelchair bound by 12 or 13 years or age.^{2,4}

Duchenne muscular dystrophy also causes dilated cardiomyopathy. The cardiomyopathy is characterized by extensive fibrosis of the posterobasal left ventricular wall. As the disease progresses, fibrosis can spread to the lateral free wall of the left ventricle. Significant mitral regurgitation is often present due to involvement of the posterior papillary muscle. Symptoms of cardiomyopathy increase gradually as the child ages into the teen years although many remain asymptomatic until the late stages of disease. The child may also develop a variety of arrhythmias and heart failure as the disease progresses.⁴

Because of increased weakness, patients with DMD are at increased risk of fractures. A study of 378 patients, ages one to twenty five years of age, with DMD found 79 percent had suffered from fractures of some kind. Most commonly the fractures were due to falling with half of them occurring among patients who were independent with ambulation.⁴

Nearly all children with DMD develop a progressive scoliosis which can result in or worsen poor pulmonary function and respiratory failure.⁴

Diagnosis – There are multiple diagnostic tests that can be used in diagnosing muscular dystrophy. Tests include: genetic testing, blood tests, electromyography (EMG), muscle biopsy, electrocardiogram (ECG), and/or echocardiograms (ECHO). The type of test(s) used are chosen based upon the type of disease that is suspected.² Children and newborns with DMD present with elevated levels of serum creatine kinase (serum CK) prior to the appearance of any clinical signs of disease. Levels peak by age two and are typically ten to twenty times higher than the normal upper limit. Once the levels have peaked they begin to fall at a rate of twenty five percent per year until they eventually reach normal limits. Aldolase levels and other muscle enzymes, such as aspartate transaminase (AST) and alanine transaminase (ALT), are also elevated in these children.⁴

In normal individuals, dystrophin levels are detected on immunoblots of 100 mcg of total muscle protein. Individuals with DMD show less than 5 percent of the normal quantity of dystrophin. Dystrophin immunoblotting may be used to predict the severity of the evolving muscular dystrophy phenotype. The quantity of the dystrophin molecule determines disease severity in DMD.⁴

Electromyography testing will show myopathic changes, usually consisting of small polyphasic potentials.⁴

Muscle biopsies demonstrate degeneration, regeneration, isolated "opaque" hypertrophic fibers and significant replacement of muscle by fat and connective tissue.⁴

Prognosis - Children with Duchenne muscular dystrophy may experience some improvement between three and six years of age. However, this is followed by gradual and persistent deterioration. The majority of patients with DMD die in their late teens or twenties. Most commonly death is due to from respiratory insufficiency or arrhythmia secondary to dilated cardiomyopathy.³

Although DMD is a progressive disease, survival, neuromuscular function, and quality of life in DMD are improving due to medical advancements and some patients are living into their thirties. Longer-term treatment with glucocorticoids, advances in respiratory care, and increased utilization of assisted ventilation are lengthening the

lives of these individuals.³

Early identification and preventative care is very important for patients with Duchenne muscular dystrophy. A Duchenne Patient Education publication found on UpToDate recommends the following for managing and preventing problems in these children:

- Pneumococcal vaccine (given once) to help prevent pneumonia, and annual influenza vaccine for children six months of age and older.
- Screening and early treatment for cardiomyopathy, starting at the time of diagnosis or around age six years.
- Lung treatment while sleeping (nocturnal noninvasive ventilation) or respiratory assistance during periods of lung infection is recommended. Lung function testing should begin around age 9 or 10 years, before the child becomes wheelchair bound, and should be repeated several times per year when lung function worsens or the child requires a wheelchair.
- Bone density should be maintained to reduce the risk of fractures by ensuring that the child has a diet rich in calcium and vitamin D. Parents should monitor their child's weight to avoid excessive weight gain and obesity; a nutritionist can assist with food planning. Vitamin D levels should be checked periodically.
- Physical therapy can help to maintain muscle function and prevent joint stiffening and contractures. Leg braces can assist with standing and walking. X-rays of the spine may be taken periodically to monitor for scoliosis after loss of ambulation.
- Surgery can help correct joint contractures, especially at the ankle. Lengthening and transferring tendons can return the joint to its normal position and prolong walking with, and sometimes even without, braces. Spinal fusion operations have been very effective in correcting scoliotic deformities and maintaining upright sitting position in a wheelchair.
- Scoliosis, or curvature of the spine, is a common complication of DMD. If severe, it can cause breathing problems and surgical treatment may be necessary. In less severe cases, braces may be effective.
- Treatment of DMD — Steroids (such as prednisone or deflazacort) are the primary treatment for DMD and are generally offered to boys who are over the age of five years. Steroids have been proven to significantly increase strength, muscle function, and lung function. Steroids also decrease the progression of scoliosis.
- Regular visits with a healthcare provider are needed to monitor the benefits and potential side effects of prednisone treatment.²

Treatment – Glucocorticoids have been the standard treatment for DMD and are offered for patients four years of age and older whose motor skills have plateaued or declined.³

Exondys 51™ – In September 2016 the U.S. Food and Drug Administration approved the first drug to treat patients with Duchenne muscular dystrophy, Exondys 51™ (eteplirsen) injection. Exondys 51™ was approved under the accelerated approval pathway, which provides for the approval of drugs that treat serious or life-threatening diseases and generally provide a meaningful advantage over existing treatments.¹

The package insert for Indications And Usage of Exondys 51™ describes the drug as an antisense oligonucleotide indicated for the treatment of Duchenne muscular dystrophy in patients with a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.⁵ This mutation is present in approximately 13 percent of patients with DMD.³

Exondys 51™ is administered once weekly as an intravenous infusion over 35 to 60 minutes. It comes as a concentrated solution that must be diluted prior to administration. The drug is indicated for pediatric use. Clinical trials have shown the most common adverse reactions were balance disorder and vomiting.⁵

Clinical Trials – The Exondys 51™ package insert contains the following clinical trial information and can be found at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/206488lbl.pdf:

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the EXONDYS 51 clinical development program, 107 patients received at least one intravenous dose of EXONDYS 51, ranging between 0.5 mg/kg (0.017 times the recommended dosage) and 50 mg/kg (1.7 times the recommended dosage). All patients were male and had genetically confirmed Duchenne muscular dystrophy. Age at study entry was 4 to 19 years. Most (89%) patients were Caucasian.

EXONDYS 51 was studied in a double-blind, placebo-controlled study for 24 weeks (Study 1), followed by an open label extension (Study 2). In Study 1, 12 patients were randomized to receive weekly intravenous infusions of EXONDYS 51 (n=8) or placebo (n=4) for 24 weeks. All 12 patients continued in Study 2 and received open-label EXONDYS 51 weekly for up to 208 weeks.

In Study 1, 4 patients received placebo, 4 patients received EXONDYS 51 30 mg/kg, and 4 patients received EXONDYS 51 50 mg/kg (1.7 times the recommended dosage). In Study 2, 6 patients received EXONDYS 51 30 mg/kg/week and 6 patients received EXONDYS 51 50 mg/kg/week.

Adverse reactions that occurred in 2 or more patients who received EXONDYS 51 and were more frequent than in the placebo group in Study 1 are presented in Table 1 (the 30 and 50 mg/kg groups are pooled). Because of the small numbers of patients, these represent crude frequencies that may not reflect the frequencies observed in practice. The 50 mg/kg once weekly dosing regimen of EXONDYS 51 is not recommended.

The most common adverse reactions were balance disorder and vomiting.

In the 88 patients who received ≥ 30 mg/kg/week of EXONDYS 51 for up to 208 weeks in clinical studies, the following events were reported in $\geq 10\%$ of patients and occurred more frequently than on the same dose in Study 1: 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 EXONDYS 51 infusion.⁵

UpToDate describes an open-label study of 19 patients with DMD and eligible dystrophin gene deletions which found that weekly intravenous administration of eteplirsen induced a dose-related increase in dystrophin production without drug-related adverse effects.³

Another 24-week placebo-controlled trial randomly assigned 12 patients (ages 7 to 13 years and ambulatory) in a 1:1:1 ratio to weekly dosing of intravenous eteplirsen 30 mg/kg, eteplirsen 50 mg/kg, or placebo. At 24 weeks this was followed by an open-label extension phase during which all subjects received eteplirsen. At 48 weeks, those assigned to eteplirsen 50 mg/kg walked a significantly greater distance in the six-minute walk test compared with the placebo/delayed eteplirsen group. At 24 weeks, muscle biopsy revealed that patients assigned to eteplirsen 30 mg/kg had an increase in dystrophin-positive fibers of 23 percent compared with no increase in the placebo group, and the difference was statistically significant. At 48 weeks, the increase in dystrophin-positive fibers for the eteplirsen 30 mg/kg and 50 mg/kg groups was 52 and 43 percent, respectively. Through week 48, there were no adverse events related to eteplirsen treatment.³

Finally UpToDate describes findings from another open-label extension phase of a study through 36 months suggested that, compared with historical controls, eteplirsen-treated patients had continued benefit on the six-minute walk test and a lower rate of loss of ambulation.³

Per the FDA's website, the FDA approval of eteplirsen has been controversial because it was based upon a trial with pronounced methodologic limitations, particularly reliance on a surrogate outcome (dystrophin in muscle biopsy) and the very small patient numbers. As part of the accelerated approval process, the FDA is requiring the manufacturer to conduct a trial to determine whether eteplirsen improves motor function of DMD patients with an amenable dystrophin gene mutation. The FDA could withdraw approval of the drug if the trial fails to show clinical benefit.³

POSITION STATEMENT

Applicable To:

- Medicaid – All Markets

Exclusions

- Female members
- Exondys 51 will not be covered for other forms of muscular dystrophy
- Members 14 years of age or older

Coverage

Initial authorization of Exondys 51™ is considered medically necessary when all of the following are met:

- Member is male under the age of 14 years old; **AND**,
- Member has a diagnosis of Duchenne Muscular Dystrophy (DMD); **AND**,
- Medication was prescribed by a neurologist who specializes in the treatment of Duchenne Muscular Dystrophy; **AND**,
- Submission of laboratory results confirming mutation of the DMD gene that is amenable to exon 51 skipping documented by:
 - a. Multiplex ligation-dependent probe amplification (MLPA); **OR**,
 - b. Array comparative genomic hybridization (array CGH); **OR**,
 - c. DMD gene sequencing; **AND**,
- Member must be ambulatory (able to walk, not wheelchair dependent); **AND**,
- Submission of baseline six minute walk test (6MWT) of ≥ 300 meters; **AND**,
- Submission of baseline BUN (blood urea nitrogen), SCr (serum creatinine), and documentation of no persistent or abnormal proteinuria; **AND**,
- Documentation of stable respiratory function (FVC predicted $> 30\%$); **AND**,
- Documentation of stable cardiac function; LVEF $> 40\%$ by ECHO; **AND**,
- Documentation of inadequate treatment response, intolerance, or contraindication to a corticosteroid (i.e. prednisone, deflazacort); **AND**,
- Prescribed dosing is no more than 30 mg/kg once weekly.

Continuation of Care of Exondys 51™ is considered medically necessary when all of the following are met:

- Patient continues to be ambulatory (able to walk); **AND**,
- Documentation of stable respiratory function (FVC predicted $> 30\%$); **AND**,
- Documentation of stable cardiac function; LVEF $> 40\%$ by ECHO; **AND**,
- Prescribed dosing is no more than 30 mg/kg once weekly.

CODING

Initial authorization: 4 weeks **Reauthorization:** 4 months

Covered HCPCS Code

J1428 Injection, eteplirsen, 10 mg

Covered ICD-10 Codes

G71.0 Muscular Dystrophy

G71.01 Duchenne or Becker muscular dystrophy

Coding information is provided for informational purposes only. The inclusion or omission of a CPT, HCPCS, or ICD-10 code does not imply member coverage or provider reimbursement. Consult the member's benefits that are in place at time of service to determine coverage (or non-coverage) as well as applicable federal / state laws.

REFERENCES

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MEDICAL POLICY COMMITTEE HISTORY AND REVISIONS

Date	Action
8/24/2018	<ul style="list-style-type: none"> • Approved by MPC. No changes.
7/6/2017	<ul style="list-style-type: none"> • Approved by MPC. New.