Pharmacy Management Drug Policy

SUBJECT: Exondys 51 (eteplirsen) for Duchenne Muscular Dystrophy (DMD)
POLICY NUMBER: PHARMACY-67
EFFECTIVE DATE: 11/22/2016
LAST REVIEW DATE: 06/03/2019

If the member's subscriber contract excludes coverage for a specific service or prescription drug, it is not covered under that contract. In such cases, medical or drug policy criteria are not applied. Medical or drug policies apply to commercial and Health Care Reform products only when a contract benefit for the specific service exists.

DESCRIPTION:

Duchenne muscular dystrophy (DMD) is a rare genetic disease that affects approximately 20,000 boys and young men in the United States. A mutation in the gene for dystrophin causes progressive muscle wasting, leading to the need for wheelchairs and ventilators. [4] There are numerous mutations in the DMD gene that have been identified and the type of mutation and its effect on the production of dystrophin accounts for variable symptoms/progression rates in each affected patient.[3,5] In general, death occurs around 19 years of age if no interventions are made.[5] Respiratory, cardiac, orthopedic, and rehabilitative interventions and the use of corticosteroids can lead to an extended life expectancy of up to 40 years. Approximately 13% of patients with DMD contain genetic mutations that are amenable to exon 51 skipping.

Exondys 51 (etiplersen) is indicated for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. It is designed to skip exon 51, allowing for the synthesis of a truncated partial functioning form of dystrophin protein. The drug is approved under accelerated approval which allows a surrogate endpoint (dystrophin level) to be used for serious disease in which there is an unmet need for therapy.

The efficacy of Exondys 51 was evaluated in three open-label pivotal studies (designated as studies 1,2,and 3 in the package insert) in patients with DMD that is amenable to exon 51 skipping. Study 1 assessed the effect of Exondys on dystrophin levels and on improved distance walked in 12 patients, Study 2 was an extension study evaluating the same patients from study 1 as compared to a matched historical control population, and study 3 is an ongoing study that included 12 different patients with DMD and studied the effect of Exondys 51 on dystrophin levels. In all 3 clinical trials, patients were required to be on stable doses of corticosteroids for at least 6 months prior to trial enrollment. Additionally, patients in all 3 clinical trials were ambulatory with a baseline minimum 6-minute walk test of at least 200 meters in study 1/2. It has been proposed that the 6MWT is a reliable tool used to measure progression in DMD.

Study 1 and 2 reported that the use of Exondys contributed to an increase in dystrophin levels and 6MWT results, however the FDA has recommended retraction of this study due to concerns related to methodology and interpretation of its findings. The FDA approval of Exondys 51 was based on results from Study 3, which reported a statistically significant increase in dystrophin levels. The median increase after 48 weeks was 0.1%. It is not yet known whether this increase in dystrophin contributes to clinical benefit in patients. The FDA labeling for Exondys 51 specifically states that a clinical benefit has not yet been established and continued approval is contingent upon verification of a clinical benefit in ongoing confirmatory clinical trials.

Following FDA approval of Exondys 51, Kinane, et al published a 2018 analysis that evaluated the effect of eteplirsen on lung function in DMD patients that participated in the aforementioned Study 1 and 2. This analysis compared Forced Vital Capacity (FVC) to historical controls from the United Dystrophinopathy Project (UDP, N=34) and Maxium Expiratory Pressure (MEP)/ Maximum Inspiratory

Pressure (MIP) were compared to published natural history. The data showed a decline in FVC of 2.3% predicted per year in eteplirsen-treated patients compared with a decline of 4.1% predicted per year in the natural history cohort. There was an annual decline in MEP% predicted of 2.6% compared to a decline of 2.7%-3.6% in historical published reports of DMD and an increase in MIP% predicted of 0.6% vs a decline of 3.8-3.8% in eteplirsen-treated patients vs historal published reports. However, this analysis only reported pulmonary function endpoints that were collected as exploratory assessments from previously reported trials (Study 1 and 2) and there are no other published prospective trials that have compared these pulmonary endpoints to an active placebo control. Due to potential heterogeneity in the historical population that was used for comparison in this analysis, the benefit of Eteplersin on pulmonary function cannot be fully assessed and the FDA labeling for Exondys 51 continues to state that a clinical benefit has not yet been established for Exondys-51.

POLICY:

Based upon our assessment and review of the peer-reviewed literature, Exondys51 has been medically proven to be effective and therefore, **medically appropriate** for the following:

1. Prescribed by or in consultation with a provider who specializes in the treatment of Duchene Muscular dystrophy (DMD) and/or neuromuscular disorders **AND**
2. Must have a diagnosis of DMD with a confirmed mutation of the DMD gene that is amenable to exon 51 skipping **AND**
3. The patient must be ambulatory with a baseline unassisted 6-minutewalk test (6MWT) of at least 200 meters
4. Recommend dosing is 30mg/kg of body weight infused once weekly
5. Initial approval for new starts will be for 3 months. Continued approval in non-new starts for additional 6-month periods will require documentation that the patient continues to be ambulatory with an unassisted 6MWT of at least 100 meters

POLICY GUIDELINES:

1. Exondys 51 is administered as an IV infusion and will be covered under the medical benefit
2. Exondys 51 will not be approved for patients who have lost ambulation. Pivotal trials only evaluated Exondys 51 in ambulatory patients and it is unknown if patients with more advanced disease and greater muscle deterioration would receive any benefit with treatment. Pivotal studies do not provide adequate support to determine if the drug provides clinical benefit related to cardiac and respiratory complications, which can lead to morbidity and mortality in DMD
3. Continued approval at time of recertification will require documentation via current progress notes (within 3 months of initial approval for new starts or 6 months of continued approval for non-new starts) that the drug is providing ongoing benefit to the patient in terms of improvement or stability in disease state or condition. Such documentation may include progress notes, imaging or laboratory findings, and other objective or subjective measures of benefit which support that continued use of the requested product is medically necessary. Also, ongoing use of the requested product must continue to reflect the current policy's preferred formulary. Recertification reviews may result in the requirement to try more cost-effective treatment alternatives as they become available (i.e.; generics, biosimilars, or other guideline-supported treatment options). Requested dosing must

continue to be consistent with FDA-approved or off-label/guideline-supported dosing recommendations.

CODES:
Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.

CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.

Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

HCPCS:
J1428 Exondys 51

UPDATES:

Date	Revision
06/2019	Revised
05/2019	P & T Approval
09/2018	Reviewed
11/2017	Reviewed
11/2016	Created

REFERENCES:

1. Sarepta Therapuetics, Inc. Exondys 51 Package Insert; September 2016
2. Mendell J, Goemans Nathalie, Lowes Linda, et al. Longitudinal Effect of Etiplirsen versus Historical Control on Ambulation in Duchenne Muscular Dystrophy. *Ann Neurol.* 2016;79:257-271
3. Annexstad EJ, Lund-Petersen I, Rasmussen M. Duchenne muscular dystrophy. *Tidsskr Nor Laegeforen.* 2014;134(14)1361-1364
4. Wood MJA. To skip or not to skip: that is the question for Duchene muscular dystrophy. *Mol Ther*. 2013; 21(12)2131-2132
5. Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. *Lancet Neurol.* 2010;9(1):77-93
6. Kinane T, Mayer O, Duda P, et al. Long-Term Pulmonary Function in Duchenne Muscular Dystrophy: Comparison of Eteplirsen-Treated Patients to Natural History. *Journal of Neuromuscular Diseases.* 2018; 5: 47-58