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Policy Number: C9941-A

Exondys 51 (eteplirsen) NC

PRODUCTS AFFECTED

Exondys 51 (eteplirsen)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:

Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:

Duchenne muscular dystrophy (DMD)

REQUIRED MEDICAL INFORMATION:

Exondys 51 (eteplirsen) is considered not medically necessary for all indications, including but not limited to Duchenne muscular dystrophy (DMD), due to insufficient evidence of therapeutic value since clinical benefit has not been established. Data from clinical studies of eteplirsen in a small number of people with DMD have demonstrated a consistent safety and tolerability profile. However, the pivotal trials were not designed to evaluate long-term safety and a clinical benefit of Exondys 51 has not been established. Molina Healthcare will be continuing to evaluate and update this policy as relevant clinical evidence becomes available to determine whether Exondys 51 (eteplirsen) provides clear clinical benefit or slows progression of the disease.

Exondys 51 (eteplirsen), once weekly IV, was approved by the U.S. Food and Drug Administration in September 2016, after a long FDA delay. The Sarepta drug was approved via FDA's accelerated approval process, which requires a confirmatory clinical trial to demonstrate efficacy.

The Sarepta confirmatory clinical trial to demonstrate efficacy is complete. A pre-press release was published in November 2021 and full results are pending.

DIAGNOSIS:

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Drug and Biologic Coverage Criteria

NA

CONTINUATION OF THERAPY:

NA

DURATION OF APPROVAL:

NA

PRESCRIBER REQUIREMENTS:

NA

AGE RESTRICTIONS:

NA

QUANTITY:

NA

PLACE OF ADMINISTRATION:

NA

DRUG INFORMATION

ROUTE OF ADMINISTRATION:

Intravenous

DRUG CLASS:

Muscular Dystrophy – Gene Therapy Agents

FDA-APPROVED USES:

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.

This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with Exondys 51. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

COMPENDIAL APPROVED OFF-LABELED USES:

None

APPENDIX

APPENDIX:

None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

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. Duchenne muscular dystrophy (DMD)

- A rare genetic disorder characterized by progressive muscle deterioration and weakness, the most common type of muscular dystrophy. DMD is caused by an absence of dystrophin, a protein that helps keep muscle cells intact.

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- An X-chromosome-linked disease recessive disorder caused by mutations (mainly deletions) in the dystrophin gene that lead to an absence or defect in the dystrophin protein, dystrophin is essential for maintenance of myocyte integrity and helps keep muscle cells intact. As males have only one X chromosome, and therefore 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.
- In U.S. estimated prevalence of DMD is 1.51-2.05 per 10,000 boys aged 5-9 years; affected children with DMD typically develop symptoms in early childhood around 3-5 years old, experiencing progressive muscle weakness and deterioration.
- Patients with DMD progressively lose the ability to perform activities independently and usually become non-ambulatory by their early teenage years and require the use of a wheelchair. As the disease progresses, life-threatening heart and respiratory conditions can occur. Patients typically succumb to the disease in their 20s or 30s; however, disease severity and life expectancy vary.
- In absence of treatment, the patient experiences: wheelchair dependence before age 13 years; death around age 20 usually due to cardiac or respiratory failure
- Disease progression in patients with DMD: Scoliosis is frequent after loss of ambulation; risk for cardiomyopathy increases with age in absence of ventilatory intervention.

Treatment Overview: Pharmacologic Agents/Conventional Therapy

There is no curative therapy, but management of disease manifestations can prolong survival and improve quality of life. A multidisciplinary team is required for management of patient with DMD and treatment options for DMD predominantly focus on management of symptoms and secondary complications. Goals of management for DMD include:

- Preserve strength, ambulation, and ventilatory and cardiac function
- Minimize of steroid complications where applicable
- Prevent and treat complications including contractures, scoliosis, ventilatory function impairment or failure, and cardiomyopathy
- Determine and arrange appropriate school environment and manage family stressors

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.

- Corticosteroids
 - DMD Care Considerations Working Group consensus guidelines urge consideration of glucocorticoid therapy (prednisone or deflazacort) for all patients with DMD (optimal dose ranges not established)
 - ♦ Goal in the ambulatory child is to preserve ambulation and minimize later respiratory, cardiac, and orthopedic complications
 - ♦ Goal of continuing glucocorticoid therapy after loss of ambulation is to preserve upper limb strength, reduce scoliosis progression, and delay declines in respiratory and cardiac function
 - Generally used to preserve ambulation and minimize complications in patients with DMD
 - In ambulatory patients, recommended if motor skills have plateaued or begun to decline
 - In non-ambulatory patients, glucocorticoids often continued if already started while ambulatory, but limited evidence regarding starting glucocorticoids
 - Daily dosing preferred over alternative regimens (alternate day, high-dose weekend, or 10-day cycles)
 - Monitor and manage side effects associated with chronic steroid therapy
- Exondys 51 (eteplirsen) is indicated for use in patients with confirmed mutation of DMD gene amenable to exon 51 skipping, however clinical improvement in motor function has not been established.
- Vitamin D and calcium supplementation suggested to manage bone health in patients with DMD
- Respiratory care including airway clearance techniques, nocturnal ventilatory support, daytime non-

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invasive ventilation, and tracheostomy may be indicated/desired as disease progresses

- For management of cardiac dysfunction, consider: Diuretics, angiotensin-converting enzyme (ACE) inhibitors, and/or beta blockers to treat manifestations of cardiac dysfunction
- Anticoagulation therapy in patients with severe cardiac dysfunction to prevent systemic thromboembolic events

Exondys 51 (eteplirsen)

- 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.
- The first drug approved to treat patients with DMD and approved under the FDA's accelerated approval program. Exondys 51 was granted FDA fast track designation, priority review, and orphan drug designation
- An antisense oligonucleotide, administered via intravenous infusion, designed to bind to exon 51 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 51 skipping. Exon skipping is intended to allow for production of an internally truncated dystrophin protein. Approximately 13% of DMD patients have amenable deletions.
- The safety and tolerability profile of eteplirsen has not included significant adverse events. The most common side effects reported by participants taking Exondys 51 in the clinical trials were balance disorder and vomiting. However, **the primary pivotal trial in support of eteplirsen's NDA consisted of only 12 patients, significantly limiting the study's power to identify potential side effects and complications from treatment.**

- Exondys 51 was granted accelerated approval based on a surrogate endpoint,[†] defined as the increase in production of the dystrophin protein in skeletal muscle, rather than measured clinical benefit. However, no correlation has been established between dystrophin levels and clinical outcomes in eteplirsen-treated patients with DMD.

[†]A "surrogate marker" can be defined as "...a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effect of the therapy."

- The FDA has concluded that the data submitted demonstrated an increase in dystrophin production that is **reasonably likely to predict clinical benefit in some patients with DMD** who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping. However, **a clinical benefit of Exondys51, including improved motor function, has not been established.** In making this decision, the FDA considered the potential risks associated with the drug, the life-threatening and debilitating nature of the disease for these children and the lack of available therapy.
- 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 directed the drug manufacturer to conduct a randomized trial to "verify [sic] the clinical benefit of eteplirsen," with a **deadline of May 2021 for submission of its results. The FDA may withdraw approval of the drug if the trial fails to show clinical benefit.**
- While eteplirsen presents a novel mechanism, its manufacturer-supported pivotal double-blind study is debatable since it's **limited to 12 patients**; 8 patients were randomized to 2 different eteplirsen doses and 4 patients were randomized to placebo for 24 weeks. The latter set of patients was then switched to eteplirsen and all were to be followed for an additional 24 weeks.
- **A clinical benefit of eteplirsen has not been established. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.**

[†]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. Approval under this pathway can be based on adequate and well-controlled studies

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showing the drug has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit to patients (how a patient feels or functions or whether they survive). This pathway provides earlier patient access to promising new drugs while the company conducts clinical trials to verify the predicted clinical benefit. Under the accelerated approval provisions, the FDA is requiring Sarepta Therapeutics to conduct a clinical trial to confirm the drug's clinical benefit. The required study is designed to assess whether Exondys 51 improves motor function of DMD patients with a confirmed mutation of the dystrophin gene amenable to exon 51 skipping. If the trial fails to verify clinical benefit, the FDA may initiate proceedings to withdraw approval of the drug.

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† to the FDA held a meeting and voted against approval of eteplirsen as treatment for DMD.

†The Peripheral and Central Nervous System Drugs Advisory Committee to the FDA discussed and voted on whether the NDA application for Exondys 51 met the statutory requirements for substantial evidence of effectiveness (April 2016). The Committee voted 7 to 6 that there was not substantial evidence to support accelerated FDA approval, although Committee members noted that there was considerable public testimony on results achieved with Exondys 51. Although the FDA is not required to follow the recommendations of its advisory committees, it generally follows the recommendations.

- A peer review article by a neurologist in UpToDate concluded that the clinical benefit of these drugs is not yet established, noting ‘*Limited data from small studies suggest that the exon 51 skipping drug eteplirsen leads to increased dystrophin in muscle and increased walking performance on timed tests in patients with a mutation of the dystrophin gene amenable to exon 51 skipping. We often prescribe eteplirsen for children with DMD who have exon 51 amenable mutations because most affected families request it, despite explanations that actual clinical benefit is unproven.*’ (Darras BT, 2019)
- Exondys 51 has been evaluated in those DMD patients who are 7 years of age or older and who are ambulatory. Future studies are required to investigate the efficacy in those DMD patients who are not ambulatory as well as in children less than 7 years of age. There is also some question as to whether cardiac and respiratory improvement may be seen with Exondys 51. This is being evaluated in future literature; however, is not clearly evaluated at this time.
- Randeree and Eslick (2018) analyzed the results of previous studies to evaluate the safety and efficacy of eteplirsen. A literature search of electronic databases was performed. The studies were limited to only human studies using eteplirsen. A total of 4 relevant clinical studies were identified. A pooled- analysis was conducted using data relating to percentage dystrophin-positive fibers obtained from muscle biopsy, and the 6 MWT. The average increase in percentage dystrophin-positive fibers after treatment with eteplirsen was 24.23 % (range of -4 to 78; SD 24.44 %). The average rate of decline in distance walked was 65 meters (range of -335 to 83; SD 100.08 m). The authors concluded that whether or not this increase in percentage dystrophin-positive fibers and distance walked was clinically significant was unclear, and there is therefore a need for more clinical trials.
- The **Institute for Clinical and Economic Review (ICER)**, published an [Evidence Report](#) assessing the comparative clinical benefit and value of the corticosteroid deflazacort (Emflaza), and two exon-skipping therapies eteplirsen (Exondys 51™) and golodirsen for the treatment DMD. ICER noted the exon- skipping therapies, eteplirsen and golodirsen, cannot be assessed for cost-effectiveness because “no persuasive evidence yet exists to demonstrate the clinical effectiveness of either drug.” ICER noted that both eteplirsen

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and golodirsen have been shown to increase production of dystrophin, which is deficient in DMD, although dystrophin levels remained very low. The best results were for golodirsen, according to the report; at 48 weeks, the mean level of dystrophin had increased to 1.019 percent of normal. There is no validated threshold in dystrophin levels associated with meaningful clinical improvement. Further, it found no evidence demonstrating improvements in muscle strength, motor function, ambulation, or pulmonary function.

- No published guidelines were identified that recommend the use of Exondys 51 for the treatment of DMD. **Limited evidence from small studies may indicate an increase in dystrophin protein with at least 24 weeks of eteplirsen therapy, but this increase did not correlate to improvement in the 6-minute walk test. Clinical benefit has not been demonstrated at 24 weeks or with use over 4 years.**

The randomized, double-blind, placebo-controlled (Study 201) was followed by an open-label extension phase in which all 12 patients received eteplirsen 30 mg/kg, weekly, by the intravenous route (Study 202). 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.

Study 201 (Mendell et al. 2013) evaluated eteplirsen for the treatment of DMD in a small, randomized, multi-center, double-blind, placebo-controlled Phase 2 study. Male patients diagnosed with DMD (n=12), aged 7 to 13 years, with confirmed deletions correctable by skipping exon 51, and a stable steroid regimen (prednisone or deflazacort) for 24 weeks to be enrolled. 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. Patients were randomized (1:1:1) to receive weekly infusions of eteplirsen (30 mg/kg, n=4); eteplirsen (50 mg/kg, n=4), or placebo (n=4) for 24 weeks (4 patients per group). Primary endpoint was dystrophin production (dystrophin-positive fibers from biopsy) and distance walked on the 6-minute walk test (6MWT, or 6-minute walk distance, 6MWD).

- Mendell et al. concluded that patients receiving eteplirsen 30 mg/kg demonstrated significant improvement in dystrophin production after 24 weeks of treatment compared with placebo, and dystrophin production continued to increase through week 48. It was reported that at week 24, dystrophin-positive fibers increased by 23% from baseline in patients treated with 30 mg/kg eteplirsen, with no significant increases in the placebo group ($p \leq 0.002$) and reported greater increases by week 48 (52% and 43% in the 30 and 50 mg/kg groups, respectively). The authors also concluded that 6 ambulation-evaluable patients taking eteplirsen demonstrated an increase in the 6MWT (67.3 m, $p \leq 0.001$) vs placebo.

However, the adjusted mean distance walked on the 6MWT by patients receiving 30 mg/kg/wk. decreased by 128.2 m from baseline to week 24 and 153.4 m from baseline to week 48, despite increases in dystrophin production. In comparison, patients receiving placebo demonstrated a 6MWT distance decrease of 25.8 m from baseline to week 24 and 68.4 m from baseline to week 48.

In contrast to the conclusions of Mendell et al, the FDA concluded that no significant difference in the change in 6MWT distance between patients treated with eteplirsen and those treated with placebo in Study 201. Study 202 failed to provide evidence of a clinical benefit when compared to the external control group (primary endpoint, week 48) (Exondys 51 FDA Summary Review 2016).

Following the 24-week study, placebo/delayed patients switched to an open-label extension treatment (Study 202) with either dosing of eteplirsen regimen. All 12 patients who participated in Study 1 (Mendell et al. 2013)† continued treatment with open-label study for an additional 4 years to evaluate the long-term efficacy and safety of eteplirsen to continue evaluation of the long-term efficacy and safety of eteplirsen (Mendell et al. 2016). Three-year progression of eteplirsen-treated patients was compared to matched historical controls.

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Since there is no control group in the open-label, long-term extension study, eteplirsen's effect on disease progression as measured by 6MWT was evaluated by comparison to matched historical controls from 2 DMD natural history cohorts: the "Italian DMD Registry" and the "Leuven Neuromuscular Reference Center" registry.

The patients participating in the extension study were compared to an external natural history control group. At Week 180 (3.5 years) of treatment, 11 patients underwent a muscle biopsy to analyze for dystrophin protein. The average dystrophin protein level after 180 weeks of treatment was 0.93% of the dystrophin level in healthy subjects. At week 24, the 30 mg/kg eteplirsen patients were biopsied, and percentage of dystrophin-positive fibers increased to 23% of normal vs. placebo ($p \leq 0.002$). At week 48, there was a 52% and 43% increase (in the 30 and 50 mg/kg/week cohorts, respectively), which suggests that dystrophin increases with longer treatment. Restoration of function dystrophin was confirmed by detection of sarcoglycans and neuronal nitric oxide synthase at the sarcolemma. Ambulation-evaluable eteplirsen-treated patients experienced a 67.3-meter benefit compared to placebo patients ($p \leq 0.001$). Both at 24 and 48 weeks, eteplirsen did not show an advantage over placebo on the 6MWD. The 6MWD data was not included in the prescribing information, because the FDA communicated that these data did not constitute substantial evidence of efficacy. The advisory committee found that these studies did not provide substantial evidence that eteplirsen induces production of dystrophin to a level that is reasonably likely to predict clinical benefit. Furthermore, the results of these historically controlled studies did not provide substantial evidence that eteplirsen is effective for the treatment of DMD. **FDA concluded, after internal review, that the extension study failed to demonstrate clinical benefit compared with the control group.**

Both studies (Mendell et al. 2013; Mendell et al. 2016) failed to meet the primary endpoints of a significant improvement in 6MWT scores, and methodological study limitations hinder the ability to interpret the efficacy of eteplirsen as a disease modifying therapy for DMD.

CONFIRMATORY STUDIES

The clinical benefit of treatment for DMD with eteplirsen, including improved motor function, has not been demonstrated. The manufacturer is required by the FDA to conduct ongoing clinical trials to establish the drug's clinical benefit. Continued approval of Exondys 51 may be contingent upon verification of a clinical benefit in these confirmatory trials [Exondys 51 (eteplirsen) prescribing information]

PROMOVI: Study of Eteplirsen in DMD Patients (Phase III Confirmatory Trial)

Study 301: An Open-Label, Multi-Center, 48-Week Study with a Concurrent Untreated Control Arm to Evaluate the Efficacy and Safety of Eteplirsen in Duchenne Muscular Dystrophy

FDA approval was also based on an ongoing, Phase 3 confirmatory trial evaluating the efficacy of eteplirsen in DMD (referenced as Study 3 in the Prescribing Information; PROMOVI, NCT02255552). PROMOVI is an open-label, multi-center 48-week study conducted in 109 ambulatory males between ages 7 to 16 years old on a stable dose of corticosteroids for at least 24 weeks. Participants with DMD amenable to exon 51 skipping were treated with the FDA approved dosing, while those with DMD not amenable to exon 51 served as controls and did not receive treatment. Patients in the treated group (DMD amenable to exon 51 skipping) received once weekly IV infusions of 30 mg/kg eteplirsen for 96 weeks, followed by a safety extension (not to exceed 48 weeks). Patients in the untreated group did not receive treatment. The primary outcome was change in 6MWT distance from baseline to 96 weeks. Data from 12 of 13 enrolled patients were available at the time of publication (prescribing information). Dystrophin levels in muscle tissue were assessed by western blot, which levels were statistically significantly increased in the active treatment arm. However, a statistically significant increase in dystrophin does not imply clinical benefit. Results at 48 weeks (N=13) showed a median increase in dystrophin levels from 0.16% at baseline to 0.44% ($p < 0.05$). The median increase after 48 weeks was 0.1%.

A pre-press release in 2021 of the full study population noted post-hoc comparator analyses to Study 201 and Study 202 were consistent to results in those studies. The PROMOVI study is limited due to its open label design and lack of a placebo comparator with mutation amenable to exon 51 skipping.

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The study completed in 2019, and full results are pending.

Continued approval for this indication may be contingent upon verification of a clinical benefit in the confirmatory trial (PROMOVI).

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Exondys 51 (eteplirsen) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Exondys 51 (eteplirsen) include: No labeled contraindications.

OTHER SPECIAL CONSIDERATIONS:

None

CODING/BILLING INFORMATION

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HCP CODE	DESCRIPTION
N/A	

AVAILABLE DOSAGE FORMS:

Exondys 51 SOLN 500MG/10ML (50mg/ml) single dose vial

Exondys 51 SOLN 100MG/2ML (50mg/ml) single dose vial

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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: References	Q2 2025
REVISION- Notable revisions: Required Medical Information References	Q2 2024
REVISION- Notable revisions: FDA-Approved Uses Background Contraindications/Exclusions/Discontinuation References	Q2 2023

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REVISION- Notable revisions: References	Q2 2022
Q2 2022 Established tracking in new format	Historical changes on file

HIGH RISK ALERT