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RECOMMENDATIONS

This policy addresses **Exondys 51 (eteplirsen)** 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. Exondys 51 is the first drug approved to treat patients with DMD.

LIMITATIONS/EXCLUSIONS: Exondys 51 (eteplirsen) is considered not medically necessary for all indications, including 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 continue 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 slated to complete in November 2020 with final data due by May 2021, according to the approval letter

SUMMARY OF EVIDENCE/POSITION

Exondys 51 (eteplirsen)

On September 19, 2016, the Food and Drug Administration (FDA) approved Exondys 51 (eteplirsen; Sarepta Therapeutics Inc.) 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.

- Exondys 51 (eteplirsen)
  - The first drug approved to treat patients with DMD and was 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.

- Thus far 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,† improvement 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."

  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.

  The sample size of the pivotal study for eteplirsen was also substantially smaller than the study sample size of a similar DMD drug, drisapersen, another antisense similar in composition to eteplirsen with a sample size of 290 from three randomized trials (two Phase 2 and one Phase 3 trial), placebo-controlled studies. Drisapersen was also granted priority review status. 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 since the studies did not demonstrate a clear benefit after 24 weeks in pre-specified clinical end points, such as changes in a 6-minute walk test. The trials also suggested the *possibility* of safety problems, including renal toxic effects and thrombocytopenia. Research and development of drisapersen has since been discontinued by the manufacturer.

- Exondys 51 was approved under the accelerated approval pathway† based on an increase in dystrophin in skeletal muscle observed in some patients treated with eteplirsen. The FDA has concluded that the data submitted by the applicant 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 Exondys 51, 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.

- **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 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 Duchenne muscular dystrophy (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 whom 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 or not 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 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.

FDA INDICATIONS

FDA-approved indication does not, in itself, dictate coverage. Molina coverage Policy may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare. The covered FDA-approved indications are conditions that are considered medically necessary; however it is not inclusive of all conditions which may be approved by the Medical Reviewer. At the discretion of the Medical Director and on a case-by-case basis, Molina Healthcare may consider authorization of the biologic therapy addressed in this Policy for members with exceptional circumstances and for members with severe disease who may fall outside of the defined criteria.

Exondys 51 is the first drug approved to treat patients with Duchenne muscular dystrophy and was approved under the FDA's accelerated approval program. Exondys 51 was granted FDA fast track designation, ‡priority review, and †orphan drug designation.

†Orphan drug designation provides incentives such as clinical trial tax credits, user fee waiver and eligibility for orphan drug exclusivity to assist and encourage the development of drugs for rare diseases.

‡The manufacturer received a rare pediatric disease priority review voucher, which comes from a program intended to encourage development of new drugs and biologics for the prevention and treatment of rare pediatric diseases. This is the seventh rare pediatric disease priority review voucher issued by the FDA since the program began.

- **Duchenne muscular dystrophy (DMD):** Eteplirsen 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, including pediatric patients.
  Orphan drug designation: Duchenne muscular dystrophy
  - This approval was based on the surrogate endpoint of increased dystrophin production in skeletal muscle, which the FDA has stated is reasonably likely to predict clinical benefit (e.g., improved motor function).
  - However, small clinical trials failed to demonstrate statistically significant clinical benefit compared to placebo, and the amount of protein produced was only a small fraction of the normal level. In one study, the median increase in truncated dystrophin was 0.1%; the average dystrophin protein level was 0.16% of normal (i.e., 0.16% of the dystrophin level in healthy subjects) before treatment and 0.44% of normal after 48 weeks of treatment. In another study, the average dystrophin protein level in muscle tissues was 0.93% of normal after 180 weeks of treatment. Nonetheless, eteplirsen offers a low-risk treatment option for patients with a rare, debilitating, and life-threatening genetic disorder. The most common adverse effects reported during clinical trials were balance disorder and vomiting.

- Additional considerations and recommendations from the FDA PI Label (2018):
  - 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.

- Most common adverse reactions listed on the FDA PI Label (2018) 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.

Available as: 50mg/mL (as 100mg/2mL or 500mg/10mL in single-dose vials)

FDA Approved: September 19, 2016

Administration & Dosage*: Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.*
- Dosage: 30 milligrams per kilogram of body weight once weekly
- Administer as an intravenous infusion over 35 to 60 minutes

Contraindications: There are no contraindications listed in the manufacturer's labeling.
Black Box Warnings/REMS: None at the time of this writing

- Special Populations (per FDA-approved labeling)
  - Geriatric Use: DMD is largely a disease of children and young adults; therefore, there is no geriatric experience with eteplirsen.
  - Lactation: There are no human or animal data to assess the effect of eteplirsen on milk production, the presence of eteplirsen in milk, or the effects of eteplirsen on the breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for eteplirsen and any potential adverse effects on the breastfed infant from eteplirsen or from the underlying maternal condition.
  - Pediatric Use: Eteplirsen is 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, including pediatric patients.
  - Pregnancy: There are no human or animal data available to assess the use of eteplirsen during pregnancy.
  - Renal or Hepatic Impairment: Eteplirsen has not been studied in patients with renal or hepatic impairment.

CLASSIFICATION: Other Miscellaneous Therapeutic Agents; Antisense oligonucleotide

COVERAGE EXCLUSIONS

Exondys 51 (eteplirsen) is considered not medically necessary for all indications, including DMD, due to insufficient evidence of therapeutic value since clinical benefit has not been established.

BACKGROUND/SUMMARY

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
- 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.

- It is the most common type of muscular dystrophy. DMD is caused by an absence of dystrophin, a protein that helps keep muscle cells intact.
- In United States, estimated prevalence of DMD is 1.51-2.05 per 10,000 boys aged 5-9 years[4]
- Associated with complete inability to produce functional dystrophin protein
- 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 occurs by, or around, age 20 years

Prognosis of DMD
- Death occurs around age 20 in absence of treatment and is 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

Other 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)[A]
    - 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-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

Clinical Evidence

SUMMARY: 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.

- Eteplirsen was evaluated in three clinical studies in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. Eteplirsen was evaluated in a number of clinical studies in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping, notably: **Study 28 and Study 33** [open-label trials evaluation eteplirsen as a single intramuscular dose (Study 33) or systemically (Study 28) at doses up to 20 mg/kg/wk for 12 weeks] and **Study 201/202,** and **PROMOVI.**

- Study 201 was a single-center, double-blind, placebo-controlled study in 12 patients with DMD. Patients were randomized (1:1:1) to eteplirsen 30 mg/kg/week, eteplirsen 50 mg/kg/week, or placebo (4 patients per group). 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.

- The endpoints for these studies can be broadly divided into those that aim to show changes in physical performance, e.g., walking speed, rise time from the floor, muscle function; and those that aim to show effects on production of dystrophin in skeletal muscle-- the surrogate endpoint. Dystrophin was quantified using two methods: Western blot and immunohistochemistry [FDA summary review. Exondys 51 injection (eteplirsen)]

Study 28: *Dose-Ranging Study of AVI-4658 (eteplirsen) to Induce Dystrophin Expression in Selected DMD Patients*[6]
Phase I, open-label, exploratory, dose-ranging, clinical trial assessing the safety, tolerability, pharmacokinetics and exploratory efficacy of eteplirsen in ambulatory individuals with DMD (n=19).

- The primary objective of the trial was to assess the safety of eteplirsen at these doses over the 26-week duration of the trial. Secondary trial objectives included assessment of plasma pharmacokinetics, urinary elimination and exploratory endpoints evaluating biological activity and clinical performance.
- Summary:
  - In a dose-finding study of male patients ages 6 to 13 years (N=19), 7 patients responded with increased dystrophin protein expression. Six of these patients received doses of 10 mg/kg or 20 mg/kg IV weekly; 2 others receiving these doses did not respond. Significant reduction of inflammatory infiltrates was also observed in cohorts treated at these doses.
  - This open-label study of 19 patients with DMD and eligible dystrophin gene deletions found that weekly intravenous administration of eteplirsen induced a dose-related increase in dystrophin production without drug-related adverse effects.
  - The FDA is requiring that the manufacturer conduct new clinical trials evaluating the clinical benefits of eteplirsen at much higher doses (e.g., 30 mg/kg/day).

STUDY 1 (Study 201)

Mendell et al. 2013

24-week, randomized, double-blind, placebo-controlled, single center study in 12 patients with DMD (Study 201). 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).

- This study evaluated the ability of eteplirsen to induce dystrophin production and improve distance walked on the 6-minute walk test (6MWT).
- 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.
- Study enrollees had muscle biopsies at baseline and week 48.
- Primary endpoint was dystrophin production (dystrophin-positive fibers from biopsy) and distance walked on the 6MWT
  - 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. 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. Therefore, FDA has concluded that a clinical benefit of eteplirsen therapy has not been demonstrated.
- Summary
  - **At 24 weeks, the mean change from baseline on the 6MWD was not significantly different between the eteplirsen and placebo groups.**
  - **FDA Commissioner recommended retraction of this study in report to senior FDA officials on September 16 and made public on the 19th:** *'The publication, now known to be misleading, should probably be retracted by its authors.'* In a footnote in the report, Califf adds: *'In view of the scientific deficiencies identified in this analysis, I believe it would be appropriate to initiate a dialogue that would lead to a formal correction or retraction (as appropriate) of the published report.*'

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 202: 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). Study 202 is a 24-week open-label extension phase during which all subjects received eteplirsen.

- Two (2) patients in the eteplirsen 30 mg/kg group became unable to ambulate soon after the study start so the study sponsor pooled the six (6) remaining eteplirsen patients (*who received eteplirsen in the 24-week double-blind phase of Study 201 and could still ambulate at the end of Study 201 and continued on open-label eteplirsen in Study 202*) and compared them to the 4 placebo patients (*originally treated with placebo in the double-blind phase of Study 201*) then later switched to open-label eteplirsen[9]
- At 24 weeks, muscle biopsy revealed that patients assigned to eteplirsen 30 mg/kg had an increase in dystrophin-positive fibers of 23% compared with no increase in the placebo group, and the difference was statistically significant. (Muscle biopsy was not done at 24 weeks for the eteplirsen 50mg/kg group).
  - 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 meter 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.

- 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.

Summary

- A number of *post hoc* analyses, comparing the 6 patients who received eteplirsen in the 24-week double-blind phase of Study 201 and could still ambulate at the end of Study 201 (and continued on open-label eteplirsen in Study 202) to those originally treated with placebo in the double-blind phase of Study 201, and later switched to open-label eteplirsen. Based on these analyses, the drug sponsor stated that "*48 weeks of treatment with eteplirsen resulted in an unprecedented and clinically meaningful 67.3-meter clinical benefit on the 6MWT compared to placebo for 24 weeks followed by eteplirsen for 24 weeks.*"
- However, considering the post-hoc nature of the analyses, the post-randomization exclusion of two patients who lost ambulation in Study 201, and the limitations of the open-label design for protecting against expectation bias on effort-dependent endpoints such as the 6MWT, **FDA indicated that data from Study 202, as presented, did not provide interpretable evidence of benefit.**[9]

STUDY 2 (Study 201/202)

Mendell et al. 2016

All 12 patients who participated in Study 1 (Mendell et al. 2013)[†] continued treatment with open-label Exondys 51 weekly 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. Three-year progression of eteplirsen-treated patients was compared to matched historical controls.[‡]

[†]In Study 1, 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). The 4 patients who had been randomized to placebo in Study 1 were re-randomized 1:1 to 30mg/kg/week (n=6) or 50mg/kg/week (n=6) at week 25 such that there were 6 patients on each dose.

[‡]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. Patients in Study 202 were attempted to be matched with patients from these two registries based on five factors: 1) corticosteroid use at baseline (use/non-use); 2) sufficient longitudinal data for 6MWT available (Y/N); 3) age ≥ 7 years (Y/N); 4) genotype amenable to any exon skipping therapy (Y/N); and 5) genotype amenable to exon 51 skipping therapy (Y/N). Patients did not have to match for baseline 6MW distance.

- All study enrollees had muscle biopsies at baseline and week 48. The surrogate endpoint was dystrophin increase in skeletal muscle in Exondys 51-treated patients.
- Efficacy measurements included dystrophin-positive fibers from biopsy and distance walked on the 6MWT.
  - Eleven (11) of the 12 patients in Study 201/202 had a fourth muscle biopsy after Week 180 (3.5 years) of treatment with eteplirsen in the continued open-label extension. The quantitative Western blot analysis showed an actual increase to only a mean (SD) of 0.9% (0.8%) of normal dystrophin levels, far less than what might be expected to provide clinical benefit.
  - It should also be noted that archived pre-treatment tissue was available for only 3 of the 11 patients. The drug sponsor supplemented these baseline samples with muscle tissue from 6 other untreated patients with DMD amenable to exon 51 skipping.
  - **Study 2 failed to provide evidence of a clinical benefit of eteplirsen compared to the external control group. The average dystrophin protein level after 180 weeks of treatment with eteplirsen was 0.93% of the dystrophin level in healthy subjects.**

Summary:
In study 201/202 (n=12) there was no statistically significant difference in a 6MWT between the placebo arm and either of two dose arms (30 mg/kg, 50 mg/kg) at 24 weeks

- In 6MWT conducted after 36 months of eteplirsen treatment on the same patients as Study 1, distance walked declined in treated patients as well as historical controls The percentage of subjects who lost ambulation ability over the 36-month period was 16.7% in the eteplirsen group (2 of 12) compared with 46.2% of historical controls (6 of 13). Lung function appeared to decline at a slower rate on pulmonary function tests compared with published data describing the natural history of DMD.
- Although the authors concluded clinically meaningful and statistically significant benefit with eteplirsen[8], the **FDA concluded, after internal review, that the extension study failed to demonstrate clinical benefit compared with the control group**.
- The average dystrophin protein level after 180 weeks of treatment was 0.93% of the dystrophin level in healthy subjects.[a]
- Significant limitations exist with the interpretation of these results due to the use of historical controls. Specifically, the historical controls may have had unknown baseline or during-treatment differences that influenced outcomes. Additionally, outcomes that are objectively and consistently measured in treated patients and historical controls may not have been recorded but are necessary for valid comparisons to be performed. Finally, the small effect size in treated patients may increase the risk of Type I error.

STUDY 1 AND STUDY 2
In the eteplirsen studies, the primary trial end point was a surrogate measure, an increase in the presence of dystrophin in muscle biopsy specimens.

Serial biopsies were performed at 12, 24, and 48 weeks, with all 12 patients were receiving drug treatment by week 48. However biopsies were performed on only half of the treated patients at each of the 12- and 24-week periods. The biopsy specimens were analyzed by scientists blinded to the patients' group assignments but not blinded to the time receiving treatment.[10] In a 2013 publication, *Mendell et al. 2013* reported results of increases to about 50% of normal in dystrophin-containing fibers in the biopsy specimens.[2] However, these results were based on an immunohistochemical assay that assessed only an increase of newly produced dystrophin compared with baseline values.

Both studies (Mendell 2013 and 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 etiplersen as a disease modifying therapy for DMD.

STUDY 3: ESSENCE (Phase III Study): ONGOING
A Double-Blind, Placebo-Controlled, Multi-Center Study with an Open-Label Extension to Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in Patients with Duchenne Muscular Dystrophy

- 13 patients were treated with open-label eteplirsen (30 mg/kg) weekly for 48 weeks and had a muscle biopsy at baseline and after 48 weeks of treatment. Patients had a mean age of 8.9 years and were on a stable dose of corticosteroids for at least 6 months.
- Dystrophin levels in muscle tissue were assessed by Western blot. In the 12 patients with evaluable results, the pre-treatment dystrophin level was 0.16% ± 0.12% (mean ± standard deviation) of the dystrophin level in a healthy subject and 0.44% ± 0.43% after 48 weeks of treatment with eteplirsen ($p < 0.05$). The median increase after 48 weeks was 0.1%. It should be noted that the clinical significance of this is unknown.

Summary: Study 3 (*summarized in the package insert*) is an unpublished, open-label trial of 13 patients with DMD receiving eteplirsen 30 mg/kg once weekly for 48 weeks. Their mean dystrophin level at baseline, expressed as a percentage of the level in healthy subjects, was 0.16%; after 48 weeks it increased to 0.44%, a statistically significant difference. The median increase was 0.1%.

At the time of this writing, the study is ongoing and still accruing patients. Interim data were obtained from patients in this study and the FDA's approval was based on the unpublished results of Study 3.

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 2018]

PROMOVI: Phase III study
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

PROMOVI is an ongoing Phase III confirmatory trial evaluating the efficacy of eteplirsen in DMD. PROMOVI is a 48-week study in patients with DMD amenable to skipping exon 51. All patients are receiving eteplirsen, 30 mg/kg/week as an IV infusion.

At the time of this review in July 2020, results have been submitted to ClinicalTrials.gov for PROMOVI; however, no study results have been posted.

- This Phase 3 confirmatory study is being conducted to provide confirmatory evidence of efficacy of eteplirsen, an investigational exon 51 skipping therapy, in DMD patients that are amenable to skipping exon 51. Additional objectives include evaluation of safety, biomarkers and the long-term effects of eteplirsen up to 96* weeks. (*Amendment to protocol updated study duration to 96 weeks.)
- 109 participants. 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.
- Subjects: Males 7-16 years with DMD.
  - Treated group (patients who are amenable to exon 51 skipping): Patient will receive weekly treatment (30 mg/kg of eteplirsen IV). Treated group must have genetic confirmation of DMD amenable to exon 51 skipping. Patients enrolled in this group will also perform functional tests and undergo laboratory work and muscle biopsies throughout the course of the study.
  - Untreated control group (patients who are not amenable to exon 51 skipping): Patients will not receive treatment with any investigational therapy and serve as a concurrent control arm. Control group will have confirmation of DMD amenable to skipping of an exon other than 51. Patients enrolled in this group will not undergo muscle biopsies but will undergo functional and laboratory tests throughout the course of the study.
- 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.
  - Primary Outcomes Measures: Change in 6MWT distance from baseline [Time Frame: Baseline, Weeks 12, 24, 36, 48]-- 6MWT distance of 300 meters or greater
  - Secondary Outcome Measures
    - The percentage of dystrophin-positive fibers [Time Frame: Baseline, Weeks 24/48/72/96]
    - Maximum inspiratory/expiratory pressure percent predicted (MIP/MEP % predicted) [Time Frame: Baseline, Weeks 12, 24, 36, 48]
  - Other Outcome Measures: Evaluate the long-term effects of eteplirsen up to 96 weeks [Time Frame: Week 1-96]

- **ESSENCE (4045-301):** Study of SRP -4045 and SRP-4053 in DMD Patients (Phase III study)
  A Double-Blind, Placebo-Controlled, Multi-Center Study with an Open-Label Extension to Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in Patients with Duchenne Muscular Dystrophy

  Intervention: Measuring the efficacy SRP-4045 and SRP-4053 compared to placebo

  Participants: Males 7-16 years with DMD amenable to exon 45 or 53 skipping. Six Minute Walk Test distance of 300-450 meters

  - The main objective of this study is to evaluate the efficacy of SRP-4045 and SRP-4053 compared to placebo in Duchenne muscular dystrophy (DMD) patients with out-of-frame deletion mutations amenable to skipping exon 45 and exon 53 respectively. Additional objectives include evaluation of safety, pharmacokinetics and biomarkers.

  - At the time of this review in July 2019, the study is posted as 'recruiting'. Estimated Study Completion Date: May 2023

ADDITIONAL STUDIES ARE BEING CONDUCTED to assess eteplirsen's efficacy in both early (ages 4-6) and more advanced (ages 7-21) stages of DMD (NCT02286947, NCT02420379).

DEFINITIONS

- 6-Minute Walk Test (6MWT): The 6MWT was developed as an integrated assessment of cardiac, respiratory, circulatory, and muscular capacity for use in clinical trials of various cardiac and pulmonary conditions. In recent years, the 6MWT has been adapted to evaluate functional capacity in neuromuscular diseases and has served as the basis for regulatory approval of a number of drugs for rare diseases, with mean changes in the 6MWT ranging from 28 to 44 meters.

- DMD gene: Human gene, which provides instructions for making the protein dystrophin (a protein that that protects muscles from deterioration). Dystrophin is located primarily in skeletal and heart muscle.
- Dystrophinopathy: spectrum of muscle disease caused by pathogenic variants of *DMD* gene that encodes dystrophin protein
  - Mild forms include asymptomatic disease with elevated serum creatine phosphokinase or muscle cramps with myoglobinuria
  - Severe forms are progressive and classified as Duchenne muscular dystrophy (DMD) or Becker muscular dystrophy

- North Star Ambulatory Assessment: a functional scale designed for ambulant boys affected by DMD

APPENDIX

Appendix 1: Guidelines

- American Academy of Neurology guideline update on corticosteroid treatment of Duchenne dystrophy can be found in Neurology 2016 Feb 2;86(5):465 or at National Guideline Clearinghouse 2016 Jun 6:50008

- American Academy of Pediatrics (AAP) policy statement on cardiovascular health supervision for individuals affected by Duchenne or Becker muscular dystrophy can be found in Pediatrics 2005 Dec;116(6):1569 full-text, reaffirmed 2008 Dec, commentary can be found in Pediatrics 2006 May;117(5):1864 full-text

- United States expert consensus guideline on diagnosis and management of Duchenne muscular dystrophy
  - Part 1: Diagnosis, pharmacological and psychosocial management can be found in Lancet Neurol 2010 Jan;9(1):77 PDF or at National Guideline Clearinghouse 2010 Aug 2:15644

- Part 2: Implementation of multidisciplinary care can be found in Lancet Neurol 2010 Feb;9(2):177 PDF or at National Guideline Clearinghouse 2010 Aug 2:15645

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HCPCS	Description
J1428	Injection, eteplirsen, 10 mg

ICD-10	Description
G71.01	Duchenne or Becker muscular dystrophy

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Annual Review* No coverage criteria changes or notable revisions with this annual reviewP&T	P&T Q4 2020

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