Washington State Health Care Authority

Exondys 51 Clinical Policy

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Washington State Health Care Authority

Overview

- Duchenne Muscular Dystrophy Background and Epidemiology
- Exondys 51 and Clinical Trials
- Clinical Policy

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Duchenne Muscular Dystrophy Background and Epidemiology

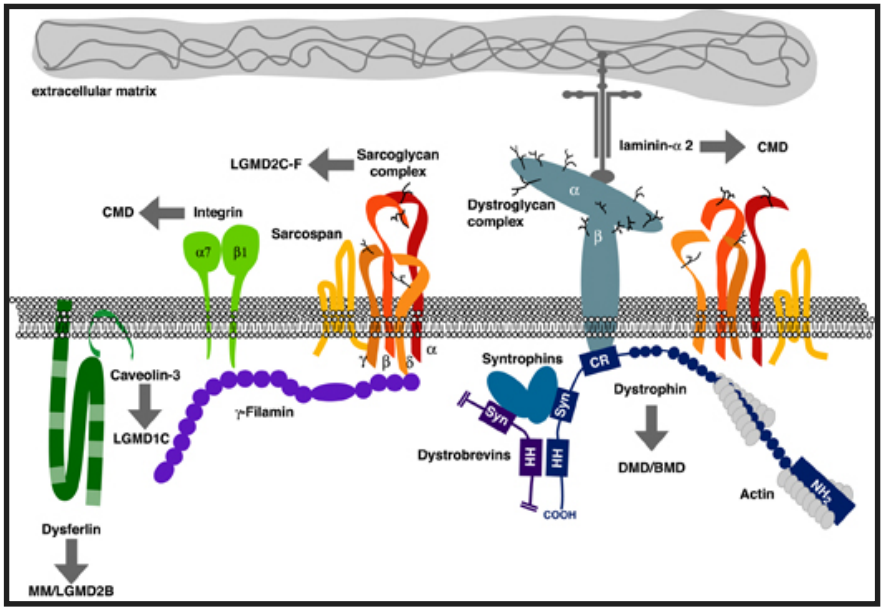
Duchenne Muscular Dystrophy (DMD)

- Duchenne muscular dystrophy (DMD) is an X-linked genetic disease affecting the dystrophin gene.

- Dystrophin is a protein that interfaces between the plasma cell membrane of muscle fibers and extracellular matrix[1].

  - Dystrophin is necessary for normal muscle function, protecting the glycoprotein complex at the membrane.

  - Loss of dystrophin results in degeneration of muscle fibers, resulting in muscle weakness, the primary symptom of DMD.



From UpToDate[1]. The dystrophin associated protein complex. Courtesy of Dr. K. O'Brien and Dr. L. Kunkel, Children's Hospital, Boston, MA.

Duchenne Muscular Dystrophy (DMD)

- DMD typically manifests as muscle weakness in males at 2 to 3 years of age[1]. Diagnosis of DMD often occurs around age 5[2].
  - Genetic tests or muscle biopsy are required to confirm diagnosis of DMD compared to other dystrophinopathies (such as Becker muscular dystrophy [BMD])[1,2].
- Muscle weakness begins in the distal limb muscles, resulting in difficulty running, jumping, and even walking[1].
  - About 82% of patients with DMD are restricted to wheelchairs between 10 through 14 years of age[2].
- Cardiomyopathy, caused by fibrosis of the left ventricular wall, can lead to heart failure and arrhythmias in the patient's teenage years[1]. Other significant medical complications from DMD are respiratory, bone fractures, and mental health.
- The most common cause of death is acute respiratory failure (due to scoliosis and progressive muscle weakness)[1]. The majority of deaths occur in the 20s.

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DMD Epidemiology

- A population-based survey in 4 US states estimates the prevalence of DMD and BMD to be 1 in 7,250 males ages 5 to 24[2]. It was estimated that, out of 2.37 million males ages 5 to 24 in 4 US states, there were 349 with DMD or BMD[3].
  - Other prevalence studies conducted in the US, Canada, Northern England, and Wales found similar population estimates[1].
- DMD has higher prevalence among Hispanics and non-Hispanic whites than among non-Hispanic blacks[2].
- The prevalence of DMD in Washington Medicaid FFS is estimated to be 100. The incidence of new DMD cases by birth is estimated to be 6.

DMD Standard of Care

- There are no approved therapies for DMD prior to Exondys 51
- Glucocorticoids can help improve motor function, pulmonary function, and reducing the risk of scoliosis in patients with DMD[1].
  - Treatment with steroids typically begins around 7 years of age[2].
  - Approximately 57% to 69% of patients with DMD and BMD are treated with steroids[2]. Prednisone is the most commonly used steroid (between 64% to 78%)[2].
- Cardiac, pulmonary, orthopedic, mental health, nutritional, growth, weight, and pain conditions are all commonly associated with DMD as well[1].

Exondys 51 and Clinical Trials

Exondys 51 (eteplirsen)

- Eteplirsen is an antisense oligonucleotide that binds to exon 51 of the dystrophin mRNA, blocking its translation during protein synthesis. This 'skipping' allows for production of internally truncated dystrophin proteins[4].
  - Approximately 13% of patients have DMD genes that are amenable to exon 51 skipping[5].
- Eteplirsen is administered by intravenous infusion at a dose of 30 mg/kg per week[4]. There is no defined end-point for when to stop therapy.

Exondys 51 (eteplirsen)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EXONDYS 51™ safely and effectively. See full prescribing information for EXONDYS 51.

EXONDYS 51 (eteplirsen) injection, for intravenous use
Initial U.S. Approval: 2016

INDICATIONS AND USAGE

EXONDYS 51 is an antisense oligonucleotide 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 *[see Clinical Studies (14)]*. 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. (1)

Study 201

- **Type:** randomized, double-blind, placebo-controlled
- **Regimens:** 30 mg/kg/week vs. 50 mg/kg/week vs. placebo
- **Demographics:** n = 4 for each subgroup (N = 12)
- **Endpoints:** 12 weeks and 24 weeks
- **Inclusion:** male with DMD and out-of-frame deletions that may be corrected by skipping exon 51; ages 7 to 13; stable cardiac and pulmonary function; oral steroids for at least 24 weeks; average distance within 180 m to 440 m walked independently over 6 minutes; LVEF >40%
- **Exclusion:** any other experimental DMD treatment; any participation in any other DMD clinical trial within 12 weeks; previous surgery within 3 months or planned surgery; clinically significant illness

Study 201 - Results

- **Dystrophin-positive fiber levels:**
  - Subjects in the 50mg/kg/wk cohort were evaluated at 12 weeks and found to have a non-statistically significant increase in dystrophin-positive fibers compared to pretreatment when compared to placebo (mean: 0.8%, range: -9.3% to 7.4%)
  - Subjects in the 30mg/kg/wk cohort were evaluated at 24 weeks and found to have a statistically significant increase in dystrophin-positive fibers compared to pretreatment when compared to placebo (mean: 22.9%, range: 15.9% to 29.0%, $p < 0.002$)
  - Actual dystrophin levels were not reported
- **6-minute walk test (6MWT):**
  - The adjusted mean for the 6MWT from baseline to 24 weeks was -25.8m (+/- 30.6) for the placebo cohort, -128.2m (+/- 31.6) for the 30mg/kg cohort and -0.3m (+/- 31.2) for the 50mg/kg cohort.

Study 202

- **Type:** randomized, open-label, extension of Study 201
- **Regimens:** 30 mg/kg/week vs. 50 mg/kg/week
- **Demographics:** n = 6 for each subgroup (N = 12)
- **Endpoints:** 24 weeks (total of 48 weeks from Study 201) and ongoing (data up to 4 years)
- **Inclusion:** participation in Study 201
- **Exclusion:** none

Study 202 - Results

- **Dystrophin-positive fiber levels:**
  - Subjects in the 30mg/kg/wk cohort and 50mg/kg/wk cohort were evaluated at 48 weeks and found to have a statistically significant increase in dystrophin-positive fibers compared to pretreatment ($p < 0.001$)
  - Subjects in the placebo cohort randomized to receive either 30mg/kg/wk or 50mg/kg/wk at 24 weeks and were evaluated at 48 weeks and found to have a statistically significant increase in dystrophin-positive fibers compared to pretreatment (mean: 37.7%, range: 28.4% to 55.1%, $p < 0.008$)
  - Actual dystrophin levels were not reported
- **6-minute walk test (6MWT):**
  - The adjusted mean for the 6MWT from baseline to 48 weeks was -68.4m (+/- 37.6) for the placebo cohort, -153.4m (+/- 38.7) for the 30mg/kg cohort and +21.0m (+/- 38.2) for the 50mg/kg cohort.

PROMOVI

- **Type:** non-randomized, open-label, untreated control arm
- **Regimens:** 30 mg/kg/week
- **Demographics:** N = 13 (still enrolling)
- **Endpoints:** 48 weeks and ongoing
- **Inclusion:** male 7-16 years old; diagnosed with DMD; stable dose of corticosteroids for at least 24 weeks; intact right and left alternative upper muscle groups; mean 6MWT greater than 300m; stable pulmonary and cardiac function; predicted FVC equal to or greater than 50% and LVEF of greater than 50%
- **Exclusion:** previous treatment with any gene therapy within the last 6 months; previous treatment with any RNA antisense agent; major surgery within 3 months; presence of clinically significant illness

PROMOVI - Results

- **Dystrophin-positive fiber levels:**
  - Western blot analysis between baseline and week 48 showed an increase from a mean of 0.16% of healthy normal subjects to a mean of 0.44% of health normal subjects for a change in a mean 0.28% (p=0.008).
- **6-minute walk test (6MWT):**
  - No information on 6MWT available at this time

Exondys 51 (eteplirsen)

- AWP for eteplirsen is set at $960 per 50 mg/mL.
- The AWP for a 50 kg patient would cost approximately $1.50 million per year.

Washington State Health Care Authority

Clinical Policy

For initial approval (24 weeks):	
Criteria	**Rationale**
Patient is diagnosed with Duchenne muscular dystrophy	FDA label and inclusion criteria for clinical trials
Patient has confirmed mutation of the DMD gene that is amenable to exon 51 skipping	
Patient is 4 years of age or older	Inclusion criteria for clinical trials
Patient has some physical function that can be maintained (e.g. upper limb function or ambulation)	
Patient is receiving glucocorticoid therapy or glucocorticoid treatment was discontinued at the recommendation of the treating physician	
Patient has stable pulmonary function (e.g. absence of invasive ventilation or tracheostomy) and cardiac function	
Medication is prescribed by or in consultation with a pediatric neurologist or other provider with expertise in treating DMD	Ensures prescriber is specialized in treatment DMD
Patient is not taking any other RNA antisense agent (e.g., drisapersen) or any other gene therapy or enrolled in any clinical trials with other investigational agents	Eteplirsen has not been studied in combination with other therapies
Exondys 51 is being prescribed at its FDA-approved dosing for 30 mg/kg once per week	Eteplirsen has not been approved for 50 mg/kg once weekly dosing
Must be receiving treatment in compliance with the DMD “standard of care” with a provider with expertise in treating DMD	

For renewal (following 24 weeks):	
Criteria	**Rationale**
Patient has observed an increase in physical function from baseline, have maintained baseline function, or progression has been slower than otherwise would have been expected in this population	Eteplirsen may not be medically necessary if clinically meaningful benefits cannot be demonstrated
Patient is receiving glucocorticoid therapy or glucocorticoid treatment was discontinued at the recommendation of the treating physician	Inclusion criteria for clinical trials
Patient has stable pulmonary function (e.g. absence of invasive ventilation or tracheostomy) and cardiac function	

Citations

1. Darras BT, Patterson MC, Firth HV, Dashe JF. Clinical features and diagnosis of Duchenne and Becker muscular dystrophy. UpToDate. Wolters Kluwer. Feb 10, 2017. https://www.uptodate.com/contents/treatment-of-duchenne-and-becker-muscular-dystrophy
2. Centers for Disease Control and Prevention (CDC). Musclar dystrophy. US Department of Health & Human Services. Jul 19, 2016. https://www.cdc.gov/ncbddd/musculardystrophy/data.html
3. Centers for Disease Control and Prevention (CDC). Musclar dystrophy. US Department of Health & Human Services. Apr 7, 2016. https://www.cdc.gov/ncbddd/musculardystrophy/facts.html
4. Exondys 51 (eteplirsen) [prescribing information]. Cambridge, MA; Sarepta Therapeutics, Inc: September 2016.
5. Food and Drug Administration (FDA). FDA grants accelerated approval to first drug for Duchenne muscular dystrophy. US Department of Health & Human Services. Sep 19, 2016. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm521263.htm
6. Breder CD, Farkas RH. NDA 206488 Sarepta eteplirsen DMD. Clinical Review. Center for Evaluation and Research. US Department of Health & Human Services. May 9, 2016.

Questions?

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