Eteplirsen (EXONDYS 51) Draft Monograph

Eteplirsen 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. 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. Efficacy:

The efficacy of eteplirsen was evaluated in three clinical trials. **Study 201** was a 24-week randomized, double-blind, placebo-controlled trial evaluating doses of 30 mg/kg/wk, 50 mg/kg/wk, and placebo in 12 patients. **Study 202** was a 24-week randomized, open-label extension study evaluating the same patients from Study 201 for long-term safety and efficacy data on 30 mg/kg/wk and 50 mg/kg/wk. The **PROMOVI** study is an ongoing, unpublished trial (ClinicalTrials.gov Identifier: NCT02255552) that was used by the FDA when evaluating the product for an increase in dystrophin in skeletal muscle.

The primary outcome measures of **Study 201** were dystrophin-positive fiber levels and a 6-minute walk test (6MWT). Subjects in the 50 mg/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 30 mg/kg/wk 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%, $p \leq 0.002$). The within-cohort results for dystrophin-positive fibers between endpoints was not statistically significant for the 50 mg/kg or placebo cohorts but were statistically significant for the 30 mg/kg cohort ($p \leq 0.004$). Actual levels of dystrophin were not reported. The adjusted mean using the MMRM model for 6MWT from baseline to 24 weeks was -25.8m (+/- 30.6) for the placebo cohort, -128.2m (+/- 31.6) for the 30 mg/kg cohort and -0.3m (+/- 31.2) for the 50 mg/kg cohort.

The primary outcome measures of **Study 202** were the same as for Study 201. The 30 mg/kg and 50 mg/kg groups saw statistically significant increases in percentage of dystrophin-positive fibers at 48 weeks ($p \leq 0.001$). The placebo cohort was randomized to receive either 30 mg/kg/wk or 50 mg/kg/wk after 24 weeks and found to have statistically significant results at 48 weeks (mean: 37.7%, range: 28.4% to 55.1%, $p \leq 0.008$). Actual levels of dystrophin were not reported. The adjusted mean using the MMRM model for 6MWT from baseline to 48 weeks was -68.4m (+/- 37.6) for the placebo cohort, -153.4m (+/- 38.7) for the 30 mg/kg cohort and +21m (+/- 38.2) for the 50 mg/kg cohort.

The primary outcome measures of the **PROMOVI** study are the same as for Study 201 and maximum inspiratory/expiratory pressure percent of predicted (MIP/MEP %). As the study is still ongoing, results are not likely to be published prior to January 2019, but a subset of data on dystrophin was used by the FDA for approval of eteplirsen. Western blot analysis between baseline and week 48 as a percentage of normal dystrophin changed from a mean 0.16% of healthy normal to 0.44% of health normal for a change in 0.28% ($p=0.008$).

2. Effectiveness:

Currently, there are no cures or disease-modifying therapies for Duchenne muscular dystrophy. Current standard of care is oral glucocorticoids. Treatment can begin as early as four years of age when symptoms related to motor skills have manifested[1]. Glucocorticoids help improve motor function and pulmonary function,

and reduce the risk of scoliosis[1]. If tolerated, glucocorticoids can be continued even after loss of ambulation. Standard of care also includes monitoring and treating other related conditions, such as cardiac disease, pulmonary complications, immunization, growth and development, and pain[1]. There are no data comparing eteplirsen and glucocorticoids as the requirement to be enrolled in the eteplirsen clinical trial included being on glucocorticoids for a minimum of 24 weeks.

In development are a number of novel therapeutics designed specifically for DMD, primarily focused on gene therapy. One other investigational drug (ataluren) is in phase III studies at this time and clinical trials have not demonstrated any meaningful clinical benefit.

3. Safety:

The safety of eteplirsen was evaluated in three clinical trials with a total of 114 patients, where 61 had received the drug for 13 weeks or longer, 36 had received it for 24 weeks or longer, and 12 had received it for 1 year or longer (up to approximately 4 years). Only 8 patients were evaluated in placebo-controlled trials (with 4 in the placebo arm and 4 in the treatment arm) for 24 weeks while the other 102 patients were observed in open-label studies. There were no deaths during clinical trials, 9 severe adverse events (SAEs) in six patients reported [none attributed to eteplirsen] and one discontinuation due to adverse events.

Eteplirsen appears to be well tolerated, but that could be attributed to the limited number of patients enrolled in placebo-controlled studies. The most frequent adverse events appear to be vomiting (38%) and balance disorder (38%).

4. Value:

To date, there are no published quality-of-life (QoL) data for eteplirsen, although the Pediatric Quality of Life Inventory was used in Study 201. Quality-of-life has been evaluated in patients with DMD, as well as their perceived QoL by their parents. It was found that patients with DMD have a lower QoL than healthy peers[2].

The AWP for eteplirsen is $960 per mL (50 mg/mL). The approved dosing for eteplirsen is 30 mg/kg once weekly, so the cost per treatment will depend on the patient's weight. Assuming that the patient weighs 30 kg, the average weekly cost would be $17,280, and the average annual cost would be $898,560. Assuming that the patient weighs 50 kg, the average weekly cost would be $28,800 and the average annual cost would be $1,497,600. Treatment is disease-modifying and has no defined end point.

5. Special Populations:

To date, eteplirsen has not been evaluated in any special populations.

Conclusion and Recommendation:

Eteplirsen is the first FDA-approved disease-modifying therapy for Duchenne muscular dystrophy that attempts to address the underlying cause of this inherited genetic disease. However, a clinical benefit of eteplirsen has not been established due to methodology issues and inconsistent results from clinical trials. One unpublished and ongoing clinical trial has demonstrated a 0.28% increase in dystrophin levels (a change in mean dystrophin of 0.16% to 0.44% of healthy normal patients [p=0.008]), but clinical trials have not demonstrated any clinically meaningful improvement in outcomes. Coupled with the high cost of treatment, I recommend that eteplirsen be considered for prior authorization with the following criteria necessary to determine approval:

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 7 years of age or older	Inclusion criteria for clinical trials
Patient is able to walk a mean distance of 300 m in the 6-minute walk test	
Patient has been on glucocorticoid therapy for at least 24 weeks	
Patient has stable pulmonary function and cardiac function	
Medication is prescribed by or in consultation with a pediatric neurologist	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

For renewal (following 24 weeks):	
Patient is ambulatory and not confined to a wheelchair	Eteplirsen may not be medically necessary if clinically meaningful benefits cannot be demonstrated
Patient has stable pulmonary function and cardiac function	
Patient is continuing glucocorticoids treatment	Inclusion criteria for clinical trials

References:

1. Darras BT, Patterson MC, Dashe JF. Treatment of Duchenne and Becker muscular dystrophy. UpToDate. Published: Oct 28, 2016. https://www.uptodate.com/contents/treatment-of-duchenne-and-becker-muscular-dystrophy

2. Uzark K, King E, Cripe L, Spicer R, Sage J, Kinnett K, Wong B, Pratt J, Varni JW. Health-related quality of life in children and adolescents with Duchenne muscular dystrophy. Pediatrics. 2012;130(6). http://pediatrics.aappublications.org/content/pediatrics/early/2012/10/30/peds.2012-0858.full.pdf