Clinical Policy: eteplirsen (Exondys 51)
Reference Number: ERX.SD.238
Effective Date: 02.15.17
Last Review Date:
Line of Business: Commercial

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Eteplirsen (Exondys 51™) is an antisense oligonucleotide.

FDA approved indication
Exondys 51 is indicated for treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

Limitation of use: 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.

Policy/Criteria
It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Exondys 51 is **not medically necessary** for its FDA-approved indication for the following reasons:

I. Eteplirsen does not have proven efficacy in the treatment of Duchenne muscular dystrophy (DMD).

A. Exondys 51 was approved based on an observed increase in dystrophin in skeletal muscle,[1] but it is unknown if that increase is clinically significant. Currently there is no clear threshold for the amount of dystrophin increase required to produce clinical benefit. Previous research has suggested dystrophin levels of at least 20-29% of normal are needed to avoid muscular dystrophy, and levels of at least 10% of normal can produce a more mild form of dystrophy.[5, 6] At week 180 of Exondys 51's pivotal study (Study 1, a 24-week randomized controlled trial, and Study 2, a 212-week open-label extension trial; N=12), eteplirsen-treated patients had mean dystrophin levels that were only 0.93% of normal per Western blot analysis.[8] In addition, a third study (Study 3, a 48-week open-label trial; N=13) found that the mean change in dystrophin from baseline after 48 weeks of treatment was 0.28% of normal per Western blot analysis; the median increase in dystrophin was 0.1%.[1]

B. **The pivotal study for approval is not reliable.** The observed increase in dystrophin was primarily measured as percentage of dystrophin-positive fibers, which does not reflect the actual quantity of dystrophin present.[4, 8] The reliability of the pivotal study for approval (Study 1 and Study 2) has been questioned by FDA Office of Drug Evaluation director Ellis Unger, MD, and FDA chief scientist Luciana Borio, MD, who both called for retraction of the study.[7]

C. **True clinical benefit has not been established.** There was no statistically significant difference in change in 6MWT distance, a clinical outcome measure used to assess disease progression, between eteplirsen-treated patients and placebo-treated patients. Of note, half of the patients receiving eteplirsen 30 mg/kg/week (n/N=2/4) lost the ability to ambulate. One of these patients continued to decline in ambulatory function despite consistent increase in dystrophin-positive fibers.[4] Furthermore, although the results of external control comparison suggest eteplirsen may slow decline of ambulation as evidenced by improvements in the 6MWT,[9] these observations are considered insufficient evidence to support clinical benefit of eteplirsen given the small sample size, variability in the DMD disease course, and known limitations with using historical control groups.

II. There is an alternative treatment option (corticosteroids; see Appendix C) with well-established efficacy in slowing decline of muscle strength and function (including motor, respiratory, and cardiac).[2, 3]

III. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
6MWT: 6-minute walk test
DMD: Duchenne muscular dystrophy
FDA: Food and Drug Administration
mRNA: messenger ribonucleic acid

Appendix B: General Information
N/A

Appendix C: Therapeutic Alternatives

Drug	Dosing Regimen	Dose Limit/ Maximum Dose
prednisone	DMD 0.3-0.75 mg/kg/day or 10 mg/kg/weekend	varies
deflazacort (Emflaza™)	DMD 0.9 mg/kg/day orally once daily	varies

IV. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose

DMD	30 mg/kg of body weight once weekly	30 mg/kg of body weight once weekly

V. Product Availability

Single-dose vial for injection: 100 mg/2 mL, 500 mg/10 mL

VI. References

1. Exondys 51 Prescribing Information. Cambridge, MA: Sarepta Therapeutics, Inc; September 2016. Available at www.exondys51.com. Accessed October 7, 2016.
2. Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol. 2010; 9(1): 77-93.
3. Gloss D, Moxley RT, Ashwal S, Oskoui M. Practice guideline update summary: corticosteroid treatment of Duchenne muscular dystrophy. Neurology. 2016; 86: 465-472.
4. Mendell JR, Rodino-Klapac LR, Sahenk Z, et al. Eteplirsen for the treatment of Duchenne muscular dystrophy. Ann Neurol. 2013; 74: 637-647.
5. Chamberlain JS. Dystrophin levels required for genetic correction of Duchenne muscular dystrophy. Basic Apply. Myol. 1997; 7(3&4): 251-255.
6. Neri M, Torelli S, Brown S, et al. Dystrophin levels as low as 30% are sufficient to avoid muscular dystrophy in the human. Neuromuscul Disord. 2007; doi:10.1016/j.nmd.2007.07.005.
7. Califf R. Scientific dispute regarding accelerated approval for Sarepta Therapeutics' eteplirsen (NDA 206488). Center for Drug Evaluation and Research. Published September 16, 2016. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_Redacted.pdf. Accessed October 20, 2016.
8. Peripheral and Central Nervous System Drugs Advisory Committee. Eteplirsen briefing document (NDA 206488). Published January 22, 2016. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM481912.pdf. Accessed September 26, 2016.
9. Mendell JR, Goemans N, Lowes LP, et al. Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy. Ann Neurol. 2016; 79: 257-271.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	12/16	12/16

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions

of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.