

Clinical Policy: Eteplirsen (Exondys 51)

Reference Number: CP.PHAR.288

Effective Date: 12.01.16

Last Review Date: 02.19

Line of Business: Commercial, HIM, Medicaid

[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

Description

Eteplirsen (Exondys 51TM) is an antisense oligonucleotide.

FDA Approved Indication(s)

Exondys 51 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.

Limitation(s) 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

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation[®] that Exondys 51 is **not medically necessary** for its FDA-approved indication:

I. Exondys 51 is not medically necessary for Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping based on the following (all of the following):

A. Eteplirsen does not have proven efficacy in the treatment of DMD.

1. **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
2. **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

3. **True clinical benefit has not been established.** There was no statistically significant difference in change in the 6-minute walk test (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 a consistent increase in dystrophin-positive fibers.⁴ Furthermore, although the results of an 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.

B. There is an alternative treatment option (corticosteroids; see Appendix B) with well-established efficacy in slowing decline of muscle strength and function (including motor, respiratory, and cardiac).^{2, 3, 10}

II. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

6MWT: 6-minute walk test

DMD: Duchenne muscular dystrophy

FDA: Food and Drug Administration

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
prednisone*	0.3-0.75 mg/kg/day or 10 mg/kg/weekend PO	Based on weight
Emflaza™ (deflazacort)	0.9 mg/kg PO QD	Based on weight

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

**Off-label*

Appendix C: Contraindications/Boxed Warnings

None reported

III. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
DMD	30 mg/kg IV once weekly	30 mg/kg

IV. Product Availability

Single-dose vial for injection: 100 mg/2 mL (50 mg/mL) and 500 mg/10 mL (50 mg/mL)

V. References

1. Exondys 51 Prescribing Information. Cambridge, MA: Sarepta Therapeutics, Inc; October 2018. Available at www.exondys51.com. Accessed November 6, 2018.
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 Appl. 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.
10. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. *Lancet Neurol.* 2018; 17: 251-267.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	12.01.16	12.16
Performed literature search: no new efficacy data is available to support use of Exondys 51 in DMD.	08.07.17	11.17
1Q18 annual review: - Policies combined for Centene Medicaid, Marketplace, and Commercial lines of business. - No significant changes. - References reviewed and updated.	10.30.17	02.18
1Q 2019 annual review: no significant changes; references reviewed and updated.	10.25.18	02.19

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note:

For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

For Health Insurance Marketplace members, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the formulary exception policy.

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