Clinical Policy: Eteplirsen

Reference Number: NH.PHAR.288
Effective Date: 12/16
Last Review Date: 12/17 Revision Log

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

Description
The intent of the criteria is to ensure that patients follow selection elements established by Centene® clinical policy for eteplirsen (Exondys 51™).

Policy/Criteria

I. It is the policy of health plans affiliated with Centene Corporation® that eteplirsen (Exondys 51) is **not medically necessary** for its FDA-approved indication for the following reasons:

A. Eteplirsen does not have proven efficacy in the treatment of Duchenne muscular dystrophy (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 misleading**. 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 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.

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]

Note: To gain approval for this medication a peer to peer review with a health plan medical director is required.

Background

Description/Mechanism of Action:

Eteplirsen is designed to bind to exon 51 of dystrophin pre-messenger ribonucleic acid (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.

Formulations:

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

FDA Approved Indications:

Exondys 51 (eteplirsen) is an antisense oligonucleotide / intravenous infusion indicated for:

- Treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

Limitations 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.

Appendices

Appendix A: Abbreviation Key

6MWT: 6-minute walk test
DMD: Duchenne muscular dystrophy
FDA: Food and Drug Administration
mRNA: messenger ribonucleic acid

Appendix B: Corticosteroid Regimens Used in DMD

- Prednisone 0.3-0.75 mg/kg/day
- Prednisone 10 mg/kg/weekend
- Deflazacort* 0.6 mg/kg/day for the first 20 days of each month
- Deflazacort* 0.9-1 mg/kg/day

**Deflazacort is not FDA-approved and is currently only available through an expanded access program.*

Reviews, Revisions, and Approvals	Date	Approval Date
New policy.	12/16	12/16
Added "To gain approval for this medication a peer to peer review with a health plan medical director is required."	4/17	4/17
Annual Review, No Changes	12/17	12/17

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.

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

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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.

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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.

Note: For Medicare members, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.

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