Clinical Policy: Eteplirsen (Exondys 51)

Reference Number: CP.PHAR.288
Effective Date: 01.01.17
Last Review Date: 02.20
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 51™) 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 may be **medically necessary*** when the following criteria are met:

**** Exondys 51 was FDA-approved based on an observed increase in dystrophin in skeletal muscle, but it is unknown if that increase is clinically significant. Continued FDA-approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.***

I. Initial Approval Criteria

A. Duchenne Muscular Dystrophy (must meet all)**:**

1. Diagnosis of DMD with mutation amenable to exon 51 skipping (*see Appendix D*) confirmed by genetic testing;
2. Prescribed by or in consultation with a neurologist;
3. Age ≤ 13 years at therapy initiation;
4. Member has all of the following assessed within the last 30 days (a, b, and c):
   a. Ambulatory function (e.g., ability to walk with or without assistive devices, not wheelchair dependent) with a 6-minute walk test (6MWT) distance ≥ 200 m;
   b. Stable cardiac function with left ventricular ejection fraction (LVEF) > 40%;
   c. Stable pulmonary function with predicted forced vital capacity (FVC) ≥ 50%;
5. Inadequate response (as evidenced by a significant decline in 6MWT, LVEF, or FVC) despite adherent use of an oral corticosteroid (e.g., prednisone, Emflaza™) for ≥ 6

months, unless contraindicated or clinically significant adverse effects are experienced;
**Prior authorization is required for Emflaza*

6. Exondys 51 is prescribed concurrently with an oral corticosteroid, unless contraindicated or clinically significant adverse effects are experienced;
7. Exondys 51 is not prescribed concurrently with other exon-skipping therapies (e.g., Vyondys 53™);
8. Dose does not exceed 30 mg/kg per week.

Approval duration: 6 months

II. Continued Therapy

A. Duchenne Muscular Dystrophy (must meet all)**:**

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Member is responding positively to therapy as evidenced by all of the following assessed within the last 30 days (a, b, and c):
   a. Ambulatory function (e.g., ability to walk with or without assistive devices, not wheelchair dependent) with a 6-minute walk test (6MWT) distance ≥ 200 m;
   b. Stable cardiac function with LVEF > 40%;
   c. Stable pulmonary function with predicted FVC ≥ 50%;
3. Exondys 51 is prescribed concurrently with an oral corticosteroid, unless contraindicated or clinically significant adverse effects are experienced;
4. Exondys 51 is not prescribed concurrently with other exon-skipping therapies (e.g., Vyondys 53);
5. If request is for a dose increase, new dose does not exceed 30 mg/kg per week.

Approval duration: 6 months

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

6MWT: 6-minute walk test
DMD: Duchenne muscular dystrophy
FDA: Food and Drug Administration
FVC: forced vital capacity
ICER: Institute for Clinical and Economic Review
LVEF: left ventricular ejection fraction

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	Based on weight
Emflaza™ (deflazacort)	0.9 mg/kg/day orally once daily	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

Appendix D: General Information

- Common mutations amenable to exon 51 skipping include: 3-50, 4-50, 5-50, 6-50, 9-50, 10-50, 11-50, 13-50, 14-50, 15-50, 16-50, 17-50, 19-50, 21-50, 23-50, 24-50, 25-50, 26-50, 27-50, 28-50, 29-50, 30-50, 31-50, 32-50, 33-50, 34-50, 35-50, 36-50, 37-50, 38-50, 39-50, 40-50, 41-50, 42-50, **43-50, 45-50, 47-50, 48-50, 49-50, 50, 52**, 52-61, 52-63, 52-64, 52-76. The bolded mutations are deletions which make up > 97% of all mutations amenable to skipping exon 51 according to the DMD registration database.
- Corticosteroids are routinely used in DMD management with established efficacy in slowing decline of muscle strength and function (including motor, respiratory, and cardiac). They are recommended for all DMD patients per the American Academy of Neurology (AAN) and DMD Care Considerations Working Group; in addition, the AAN guidelines have been endorsed by the American Academy of Pediatrics, the American Association of Neuromuscular & Electrodiagnostic Medicine, and the Child Neurology Society.
  - The DMD Care Considerations Working Group guidelines, which were updated in 2018, continue to recommend corticosteroids as the mainstay of therapy while Exondys 51 is mentioned only as an emerging treatment.
  - In an evidence report published August 2019, the Institute for Clinical and Economic Review (ICER) states that current evidence is insufficient to conclude that Exondys 51 has net clinical benefit when added to corticosteroids and supportive care versus corticosteroids and supportive care alone.
- Prednisone is the corticosteroid with the most available evidence. A second corticosteroid commonly used is deflazacort, which was FDA approved for DMD in February 2017.
- The inclusion criteria for Study 201 and Study 202, the pivotal studies used to support the FDA approval of Exondys 51, enrolled patients age 7-13 years old with a 6MWT distance ≥ 200 m, LVEF > 40%, and FVC ≥ 50% at baseline.

V. Dosage and Administration

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

VI. Product Availability

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

VII. References

1. Exondys 51 Prescribing Information. Cambridge, MA: Sarepta Therapeutics, Inc; February 2018. Available at www.exondys51.com. Accessed October 7, 2019.
2. 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.
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. 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.
6. Khan N, Eliopoulos H, Han L, et al. Eteplirsen treatment attenuates respiratory decline in ambulatory and non-ambulatory patients with Duchenne muscular dystrophy. J Neuromuscul Dis. 2019; 6(2): 213-225.
7. Institute for Clinical and Economic Review. Deflazacort, eteplirsen, and golodirsen for Duchenne muscular dystrophy: Effectiveness and value. Published August 15, 2019. Available at: https://icer-review.org/material/dmd-final-evidence-report/. Accessed October 7, 2019.
8. Sarepta Therapeutics. Amenability to exon 51 skipping. Available at: https://www.exondys51hcp.com/amenability. Accessed February 27, 2020.

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
1Q 2020 annual review: no significant changes; references reviewed and updated.	10.07.19	02.20
PA criteria added for coverage consideration when medically necessary.	02.18.20	02.20 (ad hoc)
Removed examples of positive response from Appendix D since specific measures are required in II.A.2.	05.04.20	

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.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

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.