Exon Skipping Therapies for Duchenne Muscular Dystrophy

Policy # 00542
Original Effective Date: 03/15/2017
Current Effective Date: 04/13/2020

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: deflazacort (Emflaza™)‡ is addressed separately in medical policy 00554.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of eteplirsen (Exondys 51™)‡ 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 to be **not medically necessary.****

Based on review of available data, the Company considers the use of golodirsen (Vyondys 53™)‡ for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 53 skipping to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of eteplirsen (Exondys 51) or golodirsen (Vyondys 53) for NON-FDA approved indications to be **investigational.***

Background/Overview

Exondys 51 is an antisense oligonucleotide indicated for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. The package insert notes that "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." Exondys is dosed at 30 mg/kg once weekly via an intravenous infusion. It is supplied as 100 mg and 500 mg vials.

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Vyondys 53 is also an antisense oligonucleotide indicated for the treatment of DMD, but it is for those with a mutation amenable to exon 53 skipping. Similar to Exondys 51, Vyondys 53 was approved under accelerated approval based on an increase in dystrophin protein in skeletal muscle and continued approval may be contingent upon verification of a clinical benefit in confirmatory trials. Vyondys 53 is dosed at 30 mg/kg once weekly via an intravenous infusion and is supplied as 100 mg vials.

Duchenne Muscular Dystrophy
DMD is an X linked recessive disease affecting 1 in 3,600 to 6,000 newborn male infants. Gene deletions amenable to exon 51 skipping exist in 13% of patients with DMD and genetic mutations amenable to exon 53 skipping exist in about 8% of patients with DMD. The disease is attributed to large frame-shift deletions in the DMD gene which lead to loss of dystrophin, a structural protein of muscle cells. Duchenne's is characterized by progressive proximal muscle weakness caused by muscle fiber degeneration. Of course, other comorbidities occur as well including cardiac and orthopedic issues. Without intervention, death occurs at approximately 19 years of age. With respiratory, cardiac, orthopedic, and rehabilitative interventions and use of steroids, children born today can have a life expectancy of up to 40 years.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Exondys 51 was approved for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. It should be noted that various advisory committees at the FDA voted against approval of this drug (or that it offered no effect). However, Exondys 51 was ultimately approved by the FDA in September of 2016.

Vyondys 53 was approved in December 2019 for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program

(TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Exondys 51
Exondys 51 was evaluated in three clinical studies in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 51 skipping. In the first study, 12 patients were randomized to receive weekly infusion of Exondys 51 at various doses (30 mg/kg, 50 mg/kg) versus placebo for 24 weeks. The primary endpoint was dystrophin production. The 6 minute walk test (6MWT) was also assessed. There was no significant difference in change in 6MWD between patients treated with Exondys 51 and those treated with placebo. All 12 patients who participated in the first study continued treatment with open label Exondys 51 for an additional 4 years in the second study. Patients in the second study were compared to an external control group. The primary clinical efficacy outcome was the 6MWT. Study 2 failed to provide evidence of a clinical benefit of Exondys 51 compared to the external control group. In the third study, 13 patients were treated with open-label Exondys 51 (30 mg/kg) weekly for 48 weeks and had a muscle biopsy at baseline and after 48 weeks of treatment. In the 12 patients with evaluable results, the pretreatment dystrophin level was 0.16% of the dystrophin level in a healthy subject and 0.44% after 48 weeks of treatment.

As noted in the clinical trials, Exondys 51 failed to demonstrate a clear clinical improvement in patients with DMD. This conclusion is mentioned in the FDA package insert as well: "A clinical benefit of Exondys 51 has not been established." The place in therapy and clinical efficacy of Exondys 51 will need to be established with confirmatory clinical trials.

Vyondys 53
Vyondys 53 was evaluated in one two-part study in DMD patients with a confirmed mutation of the *DMD* gene that is amenable to exon 53 skipping. Part 1 was a double-blind, placebo-controlled, dose-titration study in 12 DMD patients. Patients were randomized 2:1 to receive Vyondys 53 or matching placebo. Patients treated with Vyondys 53 received four escalating dose levels, ranging from 4 mg/kg/week to 30 mg/kg/week by intravenous infusion for 2 weeks at each dose level.

Part 2 was a 168-week, open-label study assessing the efficacy and safety of Vyondys 53 at a dose of 30 mg/kg/week in the 12 patients enrolled in part 1, plus 13 additional treatment-naïve patients with DMD amenable to exon 53 skipping. At study entry, patients had a median age of 8 years and were on a stable dose of corticosteroids for at least 6 months. Efficacy was assessed based on change

from baseline in the dystrophin protein level (measured as % of the dystrophin level in healthy subjects) at week 48 of part 2. This was assessed via muscle biopsy which was obtained at baseline prior to treatment and at week 48 of part 2. It was found that mean dystrophin levels increased from 0.1% (SD 0.07) of normal at baseline to 1.02% (SD 1.03) of normal by week 48 of part 2, with a mean change in dystrophin of 0.92% of normal levels ($p<0.001$).

Note that no results related to clinical efficacy have been reported for this drug and it remains unknown if the increase seen in dystrophin level correlates to a clinical benefit.

References

1. Exondys 51 [package insert]. Sarepta Therapeutics, Inc. Cambridge, Massachusetts. September 2016.
2. Exondys 51 Drug Evaluation. Express Scripts. September 2016.
3. Exondys 51 Prior Authorization Criteria. Express Scripts. September 2016.
4. Vyondys 53 [package insert]. Sarepta Therapeutics, Inc. Cambridge, Massachusetts. December 2019.
5. Vyondys 53 Drug Evaluation. Express Scripts. December 2019.

Policy History

Original Effective Date: 03/15/2017
Current Effective Date: 04/13/2020

03/02/2017	Medical Policy Committee review
03/15/2017	Medical Policy Implementation Committee approval. New policy.
07/01/2017	Coding update
03/01/2018	Medical Policy Committee review
03/21/2018	Medical Policy Implementation Committee approval. No change to coverage.
03/07/2019	Medical Policy Committee review
03/20/2019	Medical Policy Implementation Committee approval. No change to coverage
03/05/2020	Medical Policy Committee review
03/11/2020	Medical Policy Implementation Committee approval. Changed title to Exon Skipping Therapies for Duchenne Muscular Dystrophy and added new drug, Vyondys 53.
06/10/2020	Coding update

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09/16/2020 Coding update
Next Scheduled Review Date: 03/2021

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J1428, J3490, J3590 Add code eff 7/1/2020: J1429
ICD-10 Diagnosis	G71.00-G71.09 Added codes eff 10/1/2020: G71.20-G71.21, G71.220, G71.228, G71.29

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally

recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.