Exon Skipping Therapies for Duchenne Muscular Dystrophy

Policy # 00542
Original Effective Date: 03/15/2017
Current Effective Date: 07/01/2025

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.****

Based on review of available data, the Company considers the use of viltolarsen (Viltepso™)‡ 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.****

Based on review of available data, the Company considers the use of casimersen (Amondys 45™)‡ for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 45 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), golodirsen (Vyondys 53), viltolarsen (Viltepso), or casimersen (Amondys 45) 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 it is approved under accelerated approval based on an increase in dystrophin in skeletal

muscle observed in some patients treated with Exondys 51. 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.

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.

Viltepso is another antisense oligonucleotide indicated for the treatment of DMD in patients with a mutation amenable to exon 53 skipping. It was also approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with Viltepso. As with the other therapies, the FDA labeling indicates that continued approval may be contingent upon verification and description of clinical benefit in a confirmatory trial. Viltepso is dosed at 80 mg/kg administered once weekly as a 60-minute intravenous infusion and is supplied as 250 mg single-dose vials.

Amondys 45 is an antisense oligonucleotide indicated for the treatment of DMD in patients with a mutation amenable to exon 45 skipping. Like the others, it was approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with Amondys 45. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. Amondys 45 is dosed at 30 mg/kg administered once weekly as a 35-60 minute intravenous infusion.

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. Another 8% of patients with DMD have mutations amenable to exon 45 skipping. 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. 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.

Viltepso was approved in August 2020 for the treatment of DMD in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 53 skipping.

Amondys 45 was approved in February 2021 for the treatment of DMD in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 45 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, 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 6MWT 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.

Viltepso
Viltepso was evaluated in one multicenter, 2-period, dose-finding study in patients with a confirmed mutation in the DMD gene that is amenable to exon 53 skipping.

During the initial period (first 4 weeks) of the study, patients were randomized in a double blind fashion to Viltepso or placebo. All patients then received 20 weeks of open-label Viltepso 40 mg/kg once weekly (n= 8) or 80 mg/kg once weekly (n=8). All patients were ambulatory males age 4 to <10 years of age on a stable corticosteroid regimen for at least 3 months.

Efficacy was assessed based on change from baseline in dystrophin protein level (measured as % of the dystrophin level in healthy subjects) at Week 25. Muscle biopsies were collected from patients at baseline and following 24 weeks of Viltepso treatment and analyzed for dystrophin protein level by Western blot normalized to myosin heavy chain. In the patients who received Viltepso 80 mg/kg once weekly, mean dystrophin levels increased from 0.6% (SD 0.8) of normal at baseline to 5.9% (SD 4.5) of normal by Week 25, with a mean change in dystrophin of 5.3% (SD 4.5) of normal levels ($p=0.01$).All patients demonstrated an increase in dystrophin levels over their baseline values.

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.

Amondys 45
The efficacy of Amondys 45 on dystrophin production was evaluated in one ongoing, placebo-controlled, multicenter study in ambulatory male DMD patients with a confirmed mutation of the *DMD* gene that is amenable to exon 45 skipping. The study is planned to enroll a total of 111 patients, age 7 to 13 years, randomized to Amondys 45 or placebo in a 2 to 1 ratio. Patients were required to have been on a stable dose of oral corticosteroids for at least 24 weeks prior to dosing with Amondys 45 or placebo. Following the 96-week double-blind period, all patients began or are to begin an additional 48-week open-label treatment period. Interim 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. Interim results from 43 evaluable patients (27 in the Amondys 45 group and 16 in the placebo group) show a mean dystrophin level of 1.74% of normal in the Amondys group and 0.76% of normal in the placebo group (p=0.004).

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. July 2020.
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.
6. Viltepso [package insert]. NS Pharma, Inc. Paramus, NJ. November 2020
7. Viltepso Drug Evaluation. Express Scripts. August 2020.
8. Amondys 45 [package insert]. Sarepta Therapeutics, Inc. Cambridge, Massachusetts. February 2021.

Policy History

Original Effective Date: 03/15/2017
Current Effective Date: 07/01/2025

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

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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
09/16/2020	Coding update
03/04/2021	Medical Policy Committee review
03/10/2021	Medical Policy Implementation Committee approval. Added new drug, Viltepso to policy with relevant background information.
06/03/2021	Medical Policy Committee review
06/09/2021	Medical Policy Implementation Committee approval. Added new drug, Amondys 45 to policy with relevant background information.
06/21/2021	Coding update
06/02/2022	Medical Policy Committee review
06/08/2022	Medical Policy Implementation Committee approval. No change to coverage.
06/01/2023	Medical Policy Committee review
06/14/2023	Medical Policy Implementation Committee approval. No change to coverage.
06/06/2024	Medical Policy Committee review
06/12/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/05/2025	Medical Policy Committee review
06/11/2025	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 06/2026

Coding

The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2024 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.

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for data contained or not contained herein. Any use of CPT outside of Louisiana Blue 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.

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	J1426, J1427, J1428, J1429 Delete codes effective 07/01/2025: J3490, J3590
ICD-10 Diagnosis	All related Diagnoses

*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 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.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.