

PHARMACY / MEDICAL POLICY – 5.01.570

Pharmacologic Treatment of Duchenne Muscular Dystrophy

BCBSA Ref. Policy: 5.01.27

Effective Date: **Oct. 3, 2025***

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Replaces: N/A

*This policy has been revised.

[Click here to view the current policy.](#)

RELATED MEDICAL POLICIES:

11.01.523 Site of Service: Infusion Drugs and Biologic Agents

The Site of Service Medical Necessity criteria within this policy DOES NOT apply to Alaska fully-insured members; refer to the infusion and injection drug Medical Necessity criteria only.

Site of Service *and* the infusion and injection drug Medical Necessity criteria apply to all other plan members.

Please contact Customer Service for more information.

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Introduction

Amondys 45 (casimersen), Exondys 51 (eteplirsen), Viltepso (vitolarсен), and Vyondys 53 (golodirsen) are new drugs used for Duchenne Muscular Dystrophy (DMD), which is a rare genetic disorder characterized by progressive muscle degeneration and weakness. It is caused by an absence of a functional dystrophin, which is a protein that helps keep muscle cells intact. Dystrophin gene is thought to be defective when its structure contains one or more exon deletions due to a genetic mutation. This disease primarily affects boys. Symptom onset is

usually in early childhood, between ages 3 and 5. Muscle weakness can begin as early as age 3, first affecting the muscles of the hips, pelvic area, thighs, and shoulders, and later the skeletal (voluntary) muscles in the arms, legs, and trunk. By the early teens, the heart and respiratory muscles also get affected, often requiring the use of assistive devices. Tests used to diagnose DMD vary from a blood test (measuring creatine kinase) to the muscle biopsy (measuring dystrophin protein levels), to the genetic testing (looking for the defective dystrophin gene).

Standard of therapy is aimed at slowing the loss of muscle strength to maximize the quality of life, and involves physical therapy and medications, such as steroids: prednisone and deflazacort. Assistive devices for breathing difficulties may also be used later in the stages of disease progression. Exon skipping treatments are a novel approach used in the management of this disease.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Site of Service (SOS) Medical Necessity criteria applies ONLY to medical benefit reviews. SOS Medical Necessity criteria does NOT apply to Alaska fully-insured members; refer to the infusion and injection drug Medical Necessity criteria only. Please contact Customer Service for more information.

We will review specific intravenous (IV) and injectable drugs for medical necessity for all ages.

For those aged 13 and older, we also will review the site of service for medical necessity. Site of service is defined as the location where the drug is administered, such as a hospital-based outpatient setting, an infusion center, a physician's office, or at home. Click [here](#) to be directed to the site of service review criteria.

The following drugs addressed in this policy are subject to site of service review:



- Amondys 45 (casimersen)
- Exondys 51 (eteplirsen)
- Vyondys 53 (golodirsen)

Site of Service Administration	Medical Necessity
Medically necessary sites of service <ul style="list-style-type: none"> • Physician's office • Infusion center • Home infusion 	IV infusion and injection therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site: <ul style="list-style-type: none"> • These are the preferred medically necessary sites of service for specified drugs.
Hospital-based outpatient setting <ul style="list-style-type: none"> • Outpatient hospital IV infusion department • Hospital-based outpatient clinical level of care 	IV infusion and injection therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site. <p>This site is considered medically necessary for the first 90 days for the following:</p> <ul style="list-style-type: none"> • The initial course of infusion or injection of a pharmacologic or biologic agent <p>OR</p> <ul style="list-style-type: none"> • Re-initiation of an agent after 6 months or longer following discontinuation of therapy* <p>Note: *This does not include when standard dosing between infusions or injections is 6 months or longer.</p> <p>This site is considered medically necessary when there is no outpatient infusion center within 50 miles of the individual's home and there is no contracted home infusion agency that will travel to their home, or a hospital is the only place that offers infusions or injections of this drug.</p>



Site of Service Administration	Medical Necessity
	<p>This site is considered medically necessary only when the individual has a clinical condition which puts him or her at increased risk of complications for infusions or injections, including any 1 of the following:</p> <ul style="list-style-type: none"> • Known cardiac condition (e.g., symptomatic cardiac arrhythmia) or pulmonary condition (e.g., significant respiratory disease, serious obstructive airway disease, %FVC less than or equal to 40%) that may increase the risk of an adverse reaction • Unstable renal function which decreases the ability to respond to fluids • Difficult or unstable vascular access • Acute mental status changes or cognitive conditions that impact the safety of infusion or injection therapy • A known history of severe adverse drug reactions and/or anaphylaxis to prior treatment with a related or similar drug <p>This site is considered medically necessary when the individual has cytokine release syndrome (CRS) and all the following are met:</p> <ul style="list-style-type: none"> • CRS is grade 3 or 4 as evidenced by ALL the following: <ul style="list-style-type: none"> ○ Temperature at least 38 °C ○ Hypotension that requires 1 or more vasopressors ○ Hypoxia that requires oxygen through a high-flow nasal cannula, face mask, non-rebreather mask, or Venturi mask OR positive pressure (continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP], intubation, or mechanical ventilation) <p>AND</p> <ul style="list-style-type: none"> • The individual will be admitted into an inpatient setting as soon as possible
Hospital-based outpatient setting	These sites are considered not medically necessary for infusion and injectable therapy services of various medical and biologic



Site of Service Administration	Medical Necessity
<ul style="list-style-type: none"> • Outpatient hospital IV infusion department • Hospital-based outpatient clinical level of care 	agents when the site-of-service criteria in this policy are not met.

Drug	Medical Necessity
Antisense Oligonucleotides, IV	
Amondys 45 (casimersen) IV	<p>Amondys 45 (casimersen) is subject to review for site of service administration.</p> <p>Amondys 45 (casimersen) may be considered medically necessary for the treatment of Duchenne muscular dystrophy (DMD) when all the following are met:</p> <ul style="list-style-type: none"> • The individual is aged 21 years or younger <p>AND</p> <ul style="list-style-type: none"> • Is assigned male at birth <p>AND</p> <ul style="list-style-type: none"> • Has the diagnosis of DMD <p>AND</p> <ul style="list-style-type: none"> • Has a confirmed mutation of the DMD gene that is amenable to exon 45 skipping: <ul style="list-style-type: none"> ○ Genetic testing is required to determine the specific DMD gene mutation for a definitive diagnosis <p>AND</p> <ul style="list-style-type: none"> • Can ambulate (with or without assistance*) and complete a 6-minute-walk distance test of at least 250 meters <ul style="list-style-type: none"> ○ Record of the baseline 6MWT is necessary for the initial review <p>AND</p> <ul style="list-style-type: none"> • Has been established on a stable dose of corticosteroids for at least 3 months <p>AND</p> <ul style="list-style-type: none"> • Dose is limited to 30 mg/kg IV once weekly <p>Note: *Assistance not to include use of a wheelchair</p>

Drug	Medical Necessity
Exondys 51 (eteplirsen) IV	<p>Exondys 51 (eteplirsen) is subject to review for site of service administration.</p> <p>Exondys 51 (eteplirsen) may be considered medically necessary for the treatment of Duchenne muscular dystrophy (DMD) when all the following are met:</p> <ul style="list-style-type: none"> • The individual is aged 19 years or younger <p>AND</p> <ul style="list-style-type: none"> • Is assigned male at birth <p>AND</p> <ul style="list-style-type: none"> • Has the diagnosis of DMD <p>AND</p> <ul style="list-style-type: none"> • Has a confirmed mutation of the DMD gene that is amenable to exon 51 skipping: <ul style="list-style-type: none"> ◦ Genetic testing is required to determine the specific DMD gene mutation for a definitive diagnosis <p>AND</p> <ul style="list-style-type: none"> • Can ambulate (with or without assistance*) and complete a 6-minute-walk distance test of at least 250 meters <ul style="list-style-type: none"> ◦ Record of the baseline 6MWT is necessary for the initial review <p>AND</p> <ul style="list-style-type: none"> • Has been established on a stable dose of corticosteroids for at least 3 months <p>AND</p> <ul style="list-style-type: none"> • Dose is limited to 30 mg/kg IV once weekly <p>Note: *Assistance not to include use of a wheelchair</p>
Viltepso (vitolarsen) IV	<p>Viltepso (vitolarsen) may be considered medically necessary for the treatment of Duchenne muscular dystrophy (DMD) when all the following are met:</p> <ul style="list-style-type: none"> • The individual is aged 10 years or younger <p>AND</p> <ul style="list-style-type: none"> • Is assigned male at birth <p>AND</p> <ul style="list-style-type: none"> • Has the diagnosis of DMD

Drug	Medical Necessity
	<p>AND</p> <ul style="list-style-type: none"> Has a confirmed mutation of the DMD gene that is amenable to exon 53 skipping: <ul style="list-style-type: none"> Genetic testing is required to determine the specific DMD gene mutation for a definitive diagnosis <p>AND</p> <ul style="list-style-type: none"> Can ambulate (with or without assistance*) with a time to stand of less than 10 seconds <p>AND</p> <ul style="list-style-type: none"> Has been established on a stable dose of corticosteroids for at least 3 months <p>AND</p> <ul style="list-style-type: none"> Dose is limited to 80 mg/kg IV once weekly <p>Note: *Assistance not to include use of a wheelchair</p>
Vyondys 53 (golodirsen) IV	<p>Vyondys 53 (golodirsen) is subject to review for site of service administration.</p> <p>Vyondys 53 (golodirsen) may be considered medically necessary for the treatment of Duchenne muscular dystrophy (DMD) when all the following are met:</p> <ul style="list-style-type: none"> The individual is aged 15 years or younger <p>AND</p> <ul style="list-style-type: none"> Is assigned male at birth <p>AND</p> <ul style="list-style-type: none"> Has the diagnosis of DMD <p>AND</p> <ul style="list-style-type: none"> Has a confirmed mutation of the DMD gene that is amenable to exon 53 skipping: <ul style="list-style-type: none"> Genetic testing is required to determine the specific DMD gene mutation for a definitive diagnosis <p>AND</p> <ul style="list-style-type: none"> Can ambulate (with or without assistance*) and complete a 6-minute-walk distance test of at least 250 meters <ul style="list-style-type: none"> Record of the baseline 6MWT is necessary for the initial review



Drug	Medical Necessity
	<p>AND</p> <ul style="list-style-type: none"> Has been established on a stable dose of corticosteroids for at least 3 months <p>AND</p> <ul style="list-style-type: none"> Dose is limited to 30 mg/kg IV once weekly <p>Note: *Assistance not to include use of a wheelchair</p>
Corticosteroids, Oral	
<p>Agamree (vamorolone) oral, Emflaza (deflazacort) oral tablet and suspension</p>	<p>Agamree (vamorolone) and Emflaza (deflazacort) may be considered medically necessary if ALL the following are met:</p> <ul style="list-style-type: none"> The individual is aged 2 years or older <p>AND</p> <ul style="list-style-type: none"> Has been diagnosed with Duchenne muscular dystrophy (DMD) <p>AND</p> <ul style="list-style-type: none"> Has had an adequate trial* and treatment failure due to the lack of response or increase in adverse events with prednisone <p>AND</p> <ul style="list-style-type: none"> Has had an adequate trial* and treatment failure due to the lack of response or increase in adverse events with generic deflazacort <p>Note: *Adequate trial is defined as 3 continuous months of therapy.</p>
<p>Generic deflazacort oral tablet and suspension</p>	<p>Generic deflazacort may be considered medically necessary if ALL the following are met:</p> <ul style="list-style-type: none"> The individual is aged 2 years or older <p>AND</p> <ul style="list-style-type: none"> Has been diagnosed with Duchenne muscular dystrophy (DMD) <p>AND</p> <ul style="list-style-type: none"> Has had an adequate trial* and treatment failure due to the lack of response or increase in adverse events with prednisone <p>Note: *Adequate trial is defined as 3 continuous months of therapy.</p>
Histone Deacetylase Inhibitors, Oral	



Drug	Medical Necessity
Duvyzat (givinostat) oral	<p>Duvyzat (givinostat) may be considered medically necessary for the treatment of Duchenne muscular dystrophy when all the following are met:</p> <ul style="list-style-type: none"> • The individual is aged 6 years or older <p>AND</p> <ul style="list-style-type: none"> • Has been diagnosed with Duchenne muscular dystrophy (DMD) <p>AND</p> <ul style="list-style-type: none"> • Has a confirmed mutation of the DMD gene <p>AND</p> <ul style="list-style-type: none"> • Has been established on a stable dose of corticosteroids for at least 6 months <p>AND</p> <ul style="list-style-type: none"> • Can ambulate without a wheelchair and complete a 6-minute-walk distance test of at least 250 meters
Gene Therapy, IV	
Elevidys (delandistrogene moxeparvovec-rokl) IV	<p>Elevidys (delandistrogene moxeparvovec-rokl) may be considered medically necessary for male individuals when:</p> <ul style="list-style-type: none"> • The individual is aged 4 years or older <p>AND</p> <ul style="list-style-type: none"> • Has the diagnosis of Duchenne muscular dystrophy (DMD) <p>AND</p> <ul style="list-style-type: none"> • Has a confirmed mutation of the DMD gene: <ul style="list-style-type: none"> ◦ Genetic testing is required to determine the specific DMD gene mutation for a definitive diagnosis <p>AND</p> <ul style="list-style-type: none"> • Does not have a mutation in exon 1-17 <p>AND</p> <ul style="list-style-type: none"> • Is not on the ventilator <p>AND</p> <ul style="list-style-type: none"> • Does not have an active heart failure (ejection fraction less than 40%) <p>AND</p> <ul style="list-style-type: none"> • Can ambulate without a wheelchair and complete a 6-minute-walk distance test of at least 250 meters



Drug	Medical Necessity
	<ul style="list-style-type: none"> Record of the baseline 6MWT is necessary for the initial review <p>AND</p> <ul style="list-style-type: none"> Has been established on a stable dose of corticosteroids for at least 3 months prior and at least 30 days after gene transfer <p>AND</p> <ul style="list-style-type: none"> Has anti adeno-associated virus (AAV) serotype rh74 (anti-AAVrh74) total binding antibody titer less than 1: 400

Drug	Investigational
As listed	The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.
Agamree (vamorolone), Duvyzat (givinostat), Emflaza (deflazacort),	All other uses of Agamree (vamorolone), Duvyzat (givinostat), and Emflaza (deflazacort) for conditions not outlined in this policy are considered investigational.
Amondys 45 (casimersen), Exondys 51 (eteplirsen), Viltepso (vitolarсен), Vyondys 53 (golodirsen)	<p>All other uses of Amondys 45 (casimersen), Exondys 51 (eteplirsen), Viltepso (vitolarсен), and Vyondys 53 (golodirsen) for conditions not outlined in this policy are considered investigational, including but not limited to:</p> <ul style="list-style-type: none"> Amondys or Exondys or Viltepso or Vyondys use after Elevidys infusion
Elevidys (delandistrogene moxearvovec-rokl)	<p>All other uses of Elevidys (delandistrogene moxearvovec-rokl) for conditions not outlined in this policy are considered investigational.</p> <p>Use of Elevidys (delandistrogene moxearvovec-rokl) for the treatment of individuals who are non-ambulatory is considered investigational.</p> <p>Repeat treatment of Elevidys (delandistrogene moxearvovec-rokl) is considered investigational.</p>



Approval	Criteria
Initial authorization	<p>Non-formulary exception reviews for all drugs listed in the policy may be approved up to 12 months.</p> <p>All other reviews for Amondys 45 (casimersen), Exondys 51 (eteplirsen), Viltepso (vitolarsen), and Vyondys 53 (golodirsen) can be approved up to 12 months.</p> <p>All other reviews for Agamree (vamorolone), Duvyzat (givinostat), and Emflaza (deflazacort) can be approved up to 6 months.</p> <p>All other reviews for Elevidys (delandistrogene moxearvovec-rokl) may be approved as a one-time infusion.</p>
Re-authorization criteria	<p>Non-formulary exception reviews and all other reviews for Amondys 45 (casimersen), Exondys 51 (eteplirsen), and Vyondys 53 (golodirsen) can be approved up to 12 months and depends on the clinical benefit/response shown at the time of reauthorization, where:</p> <ul style="list-style-type: none"> • The individual does not show deterioration on 2 successive 6MWT measurements with 6 months interval over a year as compared to the baseline 6MWT measurement <p>OR</p> <ul style="list-style-type: none"> • Shows deterioration at a rate less than that expected, based on the natural history of the disease <p>Non-formulary exception reviews and all other reviews for Viltepso (vitolarsen) can be approved up to 12 months and depends on the clinical benefit/response shown at the time of reauthorization, where:</p> <ul style="list-style-type: none"> • The individual does not show deterioration on 2 successive time to stand measurements with 6 months interval over a year as compared to the baseline time to stand measurement <p>OR</p> <ul style="list-style-type: none"> • Shows deterioration at a rate less than that expected, based on the natural history of the disease

Approval	Criteria
	<p>Non-formulary exception reviews and all other reviews for Agamree (vamorolone), Duvyzat (givinostat), and Emflaza (deflazacort) can be approved up to 12 months and requires documentation of continued clinical response, measured by improvement or stable muscle strength as compared to the baseline and/or diminished loss of muscle strength.</p> <p>Non-formulary exception reviews for Elevidys (delandistrogene moxearovvec-rokl) can be approved up to 12 months. For all other reviews of Elevidys (delandistrogene moxearovvec-rokl) repeat treatment is considered investigational.</p>

Documentation Requirements

The individual's medical records submitted for review should document that medical necessity criteria are met. The record should include the following:

- Office visit notes that contain the diagnosis, relevant history, genetic testing, physical evaluation, and medication history
- Results of 6MWT tests for Amondys 45, Exondys 51, Vyondys 53 and Elevidys
- Results of time to stand measurements for Viltepso

Coding

Code	Description
HCPCS	
J1413	Injection, delandistrogene moxeparovvec-rokl, per therapeutic dose (Elevidys)
J1426	Injection, casimersen, (Amondys 45), 10 mg
J1427	Injection, viltolarsen, (Viltepso) 10 mg
J1428	Injection, eteplirsen (Exondys 51), 10 mg
J1429	Injection, golodirsen (Vyondys 53), 10 mg

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).



Related Information

Benefit Application

Agamree (vamorolone), generic deflazacort, Duvyzat (givinostat), and Emflaza (deflazacort) are managed through the pharmacy benefit. Amondys 45 (casimersen), Elevidys (delandistrogene moxeparvovec-rokl), Exondys 51 (eteplirsen), Viltepso (vitolarsen), and Vyondys 53 (golodirsen) are managed through the medical benefit.

Definition of Terms

6-Minute walk distance test (6MWD): Test that measures the distance (in meters) a person can walk in 6 minutes. This measure helps to estimate disease burden by looking at the rate of ambulation.

Antisense oligonucleotide (AON): Antisense Oligonucleotides are synthetic polymers used to alter the synthesis of a particular protein. This is achieved by the binding of the antisense oligonucleotide to the messenger RNA from which that protein is normally made.

Dystrophin gene: Dystrophin gene provides a structural link between the muscle cytoskeleton and extracellular matrix to maintain muscle integrity. Dystrophin is the largest human gene, consisting of 2.4 million base pairs of DNA (with 79 exons). It is located primarily in muscles used for movement, such as skeletal muscles, and in the heart (cardiac) muscle. Small amounts of dystrophin are also present in nerve cells in the brain. In skeletal and cardiac muscles, dystrophin is a part of a group of proteins that work together to strengthen muscle fibers and protect them from injury as muscles contract and relax. Dystrophin acts as an anchor, connecting muscle cells with other molecules outside of the cell.

Exon 45 skipping: Molecular “patch” (in the form of a drug molecule) that allows exon skipping (in this case exon #45, as that is the affected exon, which accounts for 8% of DMD individuals) to create a truncated form of a protein that is partially functional.

Exon 51 skipping: Molecular “patch” (in the form of a drug molecule) that allows exon skipping (in this case exon #51, as that is the affected exon, which accounts for 13% of DMD individuals) to create a truncated form of a protein that is partially functional.



Exon 53 skipping: Molecular “patch” (in the form of a drug molecule) that allows exon skipping (in this case exon #53, as that is the affected exon, which accounts for 8% of DMD individuals) to create a truncated form of a protein that is partially functional.

Exons: Exons are the sections of the DNA that code for the protein.

Consideration of Age

The age described in this policy for Site of Service reviews for medical necessity is 13 years of age or older. The age criterion is based on the following: Pediatric individuals are not small adults. Pediatric individuals differ physiologically, developmentally, cognitively, and emotionally from adult individuals, and vary by age groups from infancy to teen. Children often require smaller doses than adults, lower infusion rates, appropriately sized equipment, the right venipuncture site determined by therapy and age, and behavioral management during administration of care. Specialty infusion training is therefore necessary for pediatric IV insertions and therapy. Due to pediatric unique physiology and psychology, site of service review is limited to individuals above the age of 13.

Evidence Review

Background

DMD is the most common lethal X-linked genetic disorder. Progressive muscle loss with cardiac and respiratory complications are very common in DMD. Estimated prevalence of DMD is 1 in 5,000 births. Most children have elevated creatinine kinase levels at birth and develop other symptoms by the age of 2-4 years old. Before phosphorodiamidate morpholino oligomers (PMOs), estimated life expectancy was about 20 years old.

DMD is caused by a mutation in the DMD gene located on chromosome Xp21, which can lead to deletions of exons (most commonly 45-55) and ultimately result in the absence of dystrophin protein being formed in muscle fibers. Approximately 60% of all DMD individuals have intragenic deletions of one or more exons, which disrupt the reading frame of its primary transcript. Dystrophin is responsible for stabilizing the sarcolemma and protecting the muscle fibers from contraction damage and necrosis.



Glucocorticoids have been used for DMD symptom management and to slow the decline in muscle strength. Benefits of long-term glucocorticoid use for the treatment of DMD include delays in ambulation loss, preserved upper limb function, reduced risks of scoliosis and scoliosis surgery, and preserved respiratory function. However, long-term side effects can develop from prolonged glucocorticoid exposure, including fluid retention, immunosuppression, osteoporosis, impaired glucose metabolism, growth suppression, etc.

With exon skipping therapy, the exon with the DMD mutation or adjacent exon is skipped, which allows for partial restoration of dystrophin production. Antisense oligonucleotides (AOs) hybridize complementary pre-cursor mRNA sequences and regulate splice-suppressing proteins to impact gene expression. This allows for the skipping of the mutated exon during mRNA splicing, thereby restoring the reading frame and producing a truncated, but semi-functional dystrophin protein. However, AOs are easily degraded by 3' > 5' endonucleases and exonucleases, and the degradation products have the potential to be toxic to living cells and may inhibit cell proliferation. On the other hand, PMOs are charge-neutral and have minimal interaction with proteins and do not necessitate the aid of catalytic proteins for catalytic activity. Exon skipping therapy is intended for slowing the progression of DMD, converting symptoms to milder disease seen with Becker muscular dystrophy. An increase of >4% in dystrophin is thought to be necessary to increase survival in DMD.

Description

Exondys 51 (eteplirsen) is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) subclass. PMOs are synthetic molecules in which the five-membered ribofuranosyl rings found in natural DNA and RNA are replaced by a six-membered morpholino ring. Each morpholino ring is linked through an uncharged phosphorodiamidate moiety rather than the negatively charged phosphate linkage that is present in natural DNA and RNA. Each phosphorodiamidate morpholino subunit contains one of the heterocyclic bases found in DNA (adenine, cytosine, guanine, or thymine). Eteplirsen contains 30 linked subunits.

Eteplirsen is designed to bind to exon 51 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in individuals with genetic mutations that are amenable to exon 51 skipping. Exon skipping is intended to allow for production of an internally truncated dystrophin protein, which was evaluated in Study 2 and Study 3 (see below for details).



Clinical Efficacy Data and Safety

Clinical Benefit

The clinical benefit of Exondys 51 (eteplirsen) has not been established in clinical trials.

Clinical Trials Experience (Adverse Reactions)

In the Exondys 51 (eteplirsen) clinical development program, 107 individuals received at least one intravenous dose of Exondys 51, ranging between 0.5 mg/kg (0.017 times the recommended dosage) and 50 mg/kg (1.7 times the recommended dosage). All individuals were male and had genetically confirmed Duchenne muscular dystrophy. Age at study entry was 4 to 19 years. Most (89%) individuals were Caucasian.

Eteplirsen was studied in a double-blind, placebo-controlled study for 24 weeks (Study 1), followed by an open label extension (Study 2). In Study 1, 12 individuals were randomized to receive weekly intravenous infusions of Exondys 51 (n=8) or placebo (n=4) for 24 weeks. All 12 individuals continued in Study 2 and received open-label Exondys 51 weekly for up to 208 weeks.

In Study 1, 4 individuals received placebo, 4 individuals received Exondys 51 30 mg/kg, and 4 individuals received Exondys 51 50 mg/kg (1.7 times the recommended dosage). In Study 2, 6 individuals received Exondys 51 30 mg/kg/week, and 6 individuals received Exondys 51 50 mg/kg/week.

Adverse reactions that occurred in 2 or more individuals who received Exondys 51 and were more frequent than in the placebo group in Study 1 are presented in [Table 1](#) (the 30 and 50 mg/kg groups are pooled). Because of the small numbers of individuals, these represent crude frequencies that may not reflect the frequencies observed in practice. The 50 mg/kg once weekly dosing regimen of Exondys 51 is not recommended.

Table 1. Adverse Reactions in DMD Individuals Treated with 30 or 50mg/kg/week Exondys 51 with Incidence at Least 25% More than Placebo (Study 1)

Adverse Reactions	Exondys 51 (N=8) %	Placebo (N=4) %
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Balance disorder	38	0
Vomiting	38	0
Contact dermatitis	25	0

The most common adverse reactions were balance disorder and vomiting. In the 88 individuals who received ≥ 30 mg/kg/week of Exondys 51 for up to 208 weeks in clinical studies, the following events were reported in $\geq 10\%$ of individuals and occurred more frequently than on the same dose in Study 1: vomiting, contusion, excoriation, arthralgia, rash, catheter site pain, and upper respiratory tract infection. There have been reports of transient erythema, facial flushing, and elevated temperature occurring on days of Exondys 51 infusion.

Clinical Studies

Registration Trials

Exondys 51 (eteplirsen) was evaluated in three clinical studies in individuals who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

In Study 1, individuals were randomized to receive weekly infusions of Exondys 51 (30 mg/kg, n=4); Exondys 51 (50 mg/kg, n=4), or placebo (n=4) for 24 weeks. The primary endpoint was dystrophin production; a clinical outcome measure, the 6-minute walk test (6MWT), was also assessed. The 6MWT measures the distance that an individual can walk on a flat, hard surface in a period of 6 minutes. Individuals had a mean age of 9.4 years, a mean 6-minute walk distance (6MWD) at baseline of 363 meters and were on a stable dose of corticosteroids for at least 6 months. There was no significant difference in change in 6MWD between individuals treated with Exondys 51 and those treated with placebo. All 12 individuals who participated in Study 1 continued treatment with open-label Exondys 51 weekly for an additional 4 years in Study 2. The 4 individuals who had been randomized to placebo were re-randomized 1:1 to Exondys 30 or 50 mg/kg/week such that there were 6 individuals on each dose. Individuals who participated in Study 2 were compared to an external control group. The primary clinical efficacy outcome measure was the 6MWT. Eleven individuals in Study 2 had a muscle biopsy after 180 weeks of treatment with Exondys 51, which was analyzed for dystrophin protein level by Western blot. Study 2 failed to provide evidence of a clinical benefit of Exondys 51 compared to the external control group. The average dystrophin protein level after 180 weeks of treatment with EXONDYS 51 was 0.93% of the dystrophin level in healthy subjects. Because of insufficient information on



dystrophin protein levels before treatment with Exondys 51 in Study 1, it is not possible to estimate dystrophin production in response to Exondys 51 in Study 1.

Additional pulmonary endpoints were monitored in the 4-year open-label safety extension study and included measures of FVC (forced vital capacity), MIP (maximum inspiratory pressure), and MEP (maximum expiratory pressure). Loss of pulmonary function is a key contributor to mortality in individuals with DMD and this study provides clinically relevant endpoints regarding the efficacy of Exondys 51. Individuals in the Exondys 51 treated group (n=12) experienced a decline in predicted FVC by 2.3% while the natural history cohort experienced a decline of 4.1%, suggesting Exondys 51 may have a role in slowing disease progression and preserving pulmonary function.

Table 2. Western Blot Results: Exondys 51-Treated (Week 48) vs. Pre-treatment Baseline (% Normal Dystrophin)

Individual Number	Baseline % normal dystrophin	Week 48 % normal dystrophin	Change from Baseline % normal dystrophin
1	0.13	0.26	0.13
2	0.35	0.36	0.01
3	0.06	0.37	0.31
4	0.04	0.10	0.06
5	0.17	1.02	0.85
6	0.37	0.30	-0.07
7	0.17	0.42	0.25
8	0.24	1.57	1.33
9	0.11	0.12	0.01
10	0.05	0.47	0.43
11	0.02	0.09	0.07
12	0.18	0.21	0.03
Mean	0.16	0.44	0.28; p=0.008

In Study 3, 13 individuals 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. Individuals had a mean age of 8.9 years and were on a stable dose of corticosteroids for at least 6 months.

Dystrophin levels in muscle tissue were assessed by Western blot. In the 12 individuals with evaluable results, the pre-treatment dystrophin level was $0.16\% \pm 0.12\%$ (mean \pm standard deviation) of the dystrophin level in a healthy subject and $0.44\% \pm 0.43\%$ after 48 weeks of treatment with EXONDYS 51 ($p < 0.05$). The median increase after 48 weeks was 0.1%.

There were several issues with the design and execution of these studies, as discussed by Irwin and Herink (2017).

Additional Data Analyses

A systematic review by Randeree and Eslick, published March 2018, found four studies. A pooled analysis was inconclusive as to whether increase in percentage dystrophin-positive fibers and distance walked is clinically significant. The authors concluded that further evidence is required.

Kinane, et al. Published a five year follow up analysis of individuals in the original trial cohort of 12 individuals using respiratory endpoints: forced vital capacity (FVC), maximum expiratory pressure (MEP) and maximum inspiratory pressure (MIP). FVC was compared to historical controls from the United Dystrophinopathy Project (UDP, N=34), MEP and MIP were compared to published natural history rates of decline. The authors reported that their age-adjusted mixed-model repeated-measures analysis showed decreases of 2.3% and 2.6% annually for FVC% predicted and MEP% predicted, and an annual increase of 0.6% for MIP% predicted for the eteplirsen-treated cohort. Data from the UDP demonstrated a 4.1% decline in FVC% predicted.

The UDP cohort was chosen as a comparator for FVC because their data were carefully collected, and individuals were similar in demographics and treatment protocols to those in the eteplirsen trials. These data do support the conclusion that there is a decreased decline in respiratory function as measured by FVC, to approximately half that of the comparators. Although not a primary endpoint in the original trials, FVC is an appropriate marker of clinical function because end stage DMD involves the usual complications of respiratory compromise.

Amondys 45 (casimersen)

The ESSENCE trial is a Phase 3, double-blind, multi-center, randomized, placebo-controlled study that has yet to be published. The study compares the efficacy and safety of casimersen 30mg/kg IV once weekly (N=27) in males, between the ages of 7 to 21 years old, with genetically confirmed DMD amenable to exon 45 skipping, to those receiving placebo IV once

weekly (N=16) for 96 weeks. Baseline mean dystrophin protein of the individuals was 0.925% of normal, but other demographics of the individuals included in the trial have not been published. The investigators' definition of normal dystrophin protein level has not been defined. The primary endpoint is change in 6MWT from baseline, while secondary endpoints include changes in maximum inspiratory pressure % and maximum expiratory pressure % predicted from baseline at week 48, and percentage of dystrophin-positive fibers at baseline, week 24 and week 48. An open-label extension period is planned for up to Week 144 of study and the primary endpoint is the number of individuals with serious adverse events (SAEs), up to 30 days after the last infusion of casimersen. Results from an interim analysis of the ESSENCE trial at 48 weeks are listed below:

- Individuals receiving casimersen were observed to have a statistically significant increase in mean dystrophin protein levels of 1.736% of normal from baseline of 0.925% of normal ($p < 0.001$).
- Individuals receiving placebo were observed to have a statistically significant difference in mean dystrophin protein levels from baseline compared to the placebo arm ($p = 0.009$)
- There were 22 individuals who received casimersen and were tested for increased exon-skipping mRNA with RT-PCR. Each individual displayed a statistically significant increase in exon 45 skipping ($p < 0.001$) compared to baseline levels, thus a 100% response rate.
- A positive correlation between exon 45 skipping and dystrophin production was seen and statistically significant (Spearman rank correlation = 0.635, $p < 0.001$).

A Phase 1/2, randomized, double-blind, placebo-controlled, dose titration study, followed by an open-label safety and efficacy evaluation has been initiated, but no results have been reported or published. The study was expected to include 12 male individuals, ages 7 to 21 years old, with genetically confirmed DMD, amenable to exon 45 skipping with limited to no ambulation and on a stable dose of oral corticosteroids for at least 24 weeks or has undergone a corticosteroid washout period for at least 24 weeks prior to receiving casimersen. The primary endpoint is incidence of adverse events at 12 weeks and the secondary endpoint is drug concentration in the plasma at 12 weeks.

Viltepso (vitolarsen)

Viltolarsen is a phosphorodiamidate morpholino oligomer (PMO) that is designed to induce the skipping of exon 53 in the DMD primary transcript and thus restores the reading frame of the DMD gene to produce an internally deleted, partially functional dystrophin protein. The effect of

vitolarsen on dystrophin production was evaluated in one study in DMD individuals with a confirmed mutation of the DMD gene that is amenable to exon 53 skipping (Study 1). Study 1 was a multicenter, 2-period, dose-finding study conducted in the United States and Canada. During the initial period (first 4 weeks) of Study 1, individuals were randomized (double blind) to vitolarsen or placebo. All individuals then received 20 weeks of open label vitolarsen 40 mg/kg once weekly (0.5 times the recommended dosage) (N=8) or 80 mg/kg once weekly (N=8). Study 1 enrolled ambulatory male individuals 4 years to less than 10 years of age (median age 7 years) 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, i.e., % of normal) at Week 25. Muscle biopsies (left or right biceps brachii) were collected from individuals at baseline and following 24 weeks of vitolarsen treatment and analyzed for dystrophin protein level by Western blot normalized to myosin heavy chain (primary endpoint) and mass spectrometry (secondary endpoint). In individuals who received vitolarsen 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 ($p=0.01$) as assessed by validated Western blot (normalized to myosin heavy chain); the median change from baseline was 3.8%. All individuals demonstrated an increase in dystrophin levels over their baseline values. As assessed by mass spectrometry (normalized to filamin C), mean dystrophin levels increased from 0.6% (SD 0.2) of normal at baseline to 4.2% (SD 3.7) of normal by Week 25, with a mean change in dystrophin of 3.7% (SD 3.8) of normal levels (nominal $p=0.03$, not adjusted for multiple comparisons); the median change from baseline was 1.9%.

Vyondys 53 (golodirsen)

Golodirsen has been studied in a single, unpublished, Phase 1/2 trial, Study 101. Part 1 consisted of a 12-week, double-blind, placebo-controlled, Phase 1 study which randomized 12 boys with genetically confirmed DMD amenable to exon 53 skipping to golodirsen or placebo. The individuals were 6-15 years of age with mean 6MWT of ≥ 250 meters, and stable pulmonary and cardiac function. Those randomized to golodirsen received 4 mg/kg IV weekly for 2 weeks, followed by 10, 20, and 30 mg/kg each for 2 weeks. The primary outcome measures were AEs and serious adverse events (SAEs). All individuals reported at least one treatment-emergent adverse event (TEAE); however, these were not described. No severe TEAE or discontinuations due to AEs occurred. Moderate TEAE occurred in two individuals (pyrexia and a *Staphylococcus aureus* Port-A-Cath infection). No further safety results were provided. Secondary outcome measures found the time to maximum concentration (T_{max}) of golodirsen was 1.01-1.22 hours and the half-life ranged from 3.2-3.4 hours.



Part 2 of Study 101 consisted of a 144-week, open-label, Phase 2 trial conducted in 25 individuals treated with golodirsen. All individuals from the Phase 1 trial continued to the Phase 2 trial. Additionally, 24 individuals with DMD who were not amenable to exon 53 skipping were included as an untreated group. The co-primary outcomes were change from BL in total distance walked in the 6MWT at week 144 and change from BL in dystrophin protein level at week 48. The 6MWT results are not yet available. Golodirsen significantly increased the mean (\pm SD) change in percent normal dystrophin at week 48 compared to BL ($1.02\% \pm 1.03\%$ (range 0.09%-4.3%) vs $0.095\% \pm 0.068\%$ (range 0.02%-0.31%) golodirsen vs BL, mean change $0.92\% \pm 1.01$, $p < 0.001$). This was a 16-fold increase in dystrophin compared to BL. Median change from BL was 0.88%. No data from the untreated group was reported. Secondary outcome measures in Part 2 of Study 101 found exon 53 skipping increased from 2.6% at BL to 19% at week 48. A positive correlation was noted between exon skipping and dystrophin expression ($r = 0.5$, $p = 0.011$). Restoration of the reading frame was confirmed in all individuals who were assessed via Sanger deoxyribonucleic acid (DNA) sequence analysis of polymerase chain reaction (PCR)-amplified products (n not reported). The mean \pm SD percentage of dystrophin-positive fibers (PDPF) at week 48 was $10.47\% \pm 10.10\%$ with golodirsen compared to $1.43\% \pm 2.04$ at BL ($p < 0.001$).

Elevidys (delandistrogene moxeparvovec-rokl)

Elevidys is an adeno-associated virus vector-based gene therapy, which is indicated for the treatment of ambulatory pediatric individuals aged 4 through 5 years of age with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the DMD gene.

Elevidys is the recombinant gene therapy product that is comprised of non-replicating, recombinant, adeno-associated virus (AAV) serotype rh74 capsid and a ssDNA expression cassette flanked by inverted terminal repeats (ITRs) derived from AAV2.

The efficacy and safety of Elevidys was evaluated in study 1 and 2. Study 1 is an ongoing multi-center study. This study has part 1 and part 2. Part 1 of the trial was a 48 week, randomized, double-blind, placebo-controlled study. Individuals who received placebo in the first part of the study received Elevidys during the second part of the study. Similarly, individuals who received Elevidys in the first part of the study received placebo during the second part of the study. The study included 41 pediatric male individuals between the age of 4 to 7 years old with either a confirmed frameshift mutation, or a premature stop codon mutation between exons 18 to 58 in the DMD gene. In this trial, the individuals were randomized 1:1 to receive either Elevidys or placebo as a single IV infusion via a peripheral limb.



In the study individuals, one day prior to receiving Elevidys or placebo, the individual's baseline corticosteroid dose was increased to at least 1 mg/kg of a corticosteroid daily and was continued at this level for at least 60 days after the infusion.

The primary efficacy endpoint of the study was to evaluate expression of Elevidys micro-dystrophin in the skeletal muscle and to evaluate the effect of Elevidys on the North Star Ambulatory Assessment (NSAA) total score.

At the end of the study 1, the NSAA total score change was not statistically significant for the individuals in age group of 4 to 7 years old. However, exploratory subgroup analysis showed that for all the subjects through 4 to 5 years, the least square mean changes in NSAA total score from baseline to week 48 was 4.3 points in the Elevidys group compared to the least square mean change in NSAA total score from baseline to week 48 was 1.9 points in the placebo group.

Study 2 is an ongoing , open label, multi-center study where 20 ambulatory male aged 4 through 7 years with DMD were included in the study. All 20 individuals have a confirmed frameshift mutation, canonical splice site mutation, or premature stop codon mutation in the DMD gene. The primary efficacy endpoint was study is evaluating expression of Elevidys micro-dystrophin in the skeletal muscle.

The mean change of micro-dystrophin expression from baseline to end of part 1 of study 1 was 43.4, while mean change of micro-dystrophin expression from baseline to end of part 2 of study 1 was 40.7. In study 2, the mean change of micro-dystrophin expression from baseline to end of study 2 was 54.2.

The most common adverse events were vomiting, nausea, elevated levels of liver function tests, pyrexia, and thrombocytopenia. The severe adverse events include but not limited to acute serious liver injury, immune-mediated myositis and myocarditis.

Agamree (vamorolone)

Agamree (vamorolone) is a dissociative corticosteroidal anti-inflammatory drug that binds to the same target receptors as the corticosteroid class (glucocorticoid receptor, mineralocorticoid receptor), but has a different chemical structure. It was designed without a 11 β -hydroxyl/carbonyl moiety on the steroidal C ring, changing the structure and activity relationships with the glucocorticoid receptor and mineralocorticoid receptor compared to the active forms of prednisone and deflazacort. It is postulated that the disruption of the ligand hydrogen bond allows vamorolone to retain transrepression activity (anti-inflammatory effects) and reduce transactivation activity (adverse effects). In addition, vamorolone cannot be acted on



by modulatory 11 β -hydroxysteroid dehydrogenase enzymes shown to be necessary for mediating corticosteroid-associated bone morbidities in mice. Lastly, vamorolone is an antagonist of the mineralocorticoid receptor, whereas most corticosteroids are agonists. The approval of Agamree was based on data from the Phase 2b, randomized, double-blind, placebo-controlled VISION-DMD trial, supplemented by safety data from three open-label studies. In the VISION-DMD study, Agamree met the primary endpoint, time-to-stand test (TTSTAND) velocity at 6 mg/kg/day versus placebo at 24 weeks of treatment ($P = 0.002$), and key secondary endpoints were also met for the Agamree 6 mg/kg/day group. The Agamree 2 mg/kg/day treatment group showed statistically significant improvements versus placebo in TTSTAND and 6MWT but not time to run/walk (TTRW). Hierarchical testing ended prior to the sixth- and seventh-ranked secondary efficacy endpoints, which compared Agamree to prednisone.

Duvyzat (givinostat)

The approval of Duvyzat is based on the results of the pivotal Phase 3 EPIDYS trial (NCT02851797). In the randomized, double-blind, placebo-controlled study, 179 ambulant boys between 6 and 17 years of age with DMD were randomly assigned (2:1) to either oral Duvyzat twice daily or placebo, in addition to standard-of-care (SOC) corticosteroids, for an 18-month treatment period. Results demonstrated that individuals who received Duvyzat showed a slower decline on the primary endpoint of four-stair climb (4SC) assessment versus those who received placebo. Duvyzat also showed favorable results on key secondary endpoints, including North Star Ambulatory Assessment (NSAA) and fat infiltration evaluation by magnetic resonance imaging. The most common adverse reactions ($\geq 10\%$ in Duvyzat-treated individuals) were diarrhea, abdominal pain, thrombocytopenia, nausea/vomiting, hypertriglyceridemia, and pyrexia. An ongoing extension study (NCT03373968) is evaluating the long-term safety and efficacy of Duvyzat. The prescribing information for Duvyzat includes warnings, including monitoring and dosage modification or permanent discontinuation, related to low platelet counts, high triglycerides, moderate or severe diarrhea, and prolonged QTc intervals.

Practice Guidelines and Position Statements

Per the recommendations from the Report of the Guideline Development Subcommittee of the American Academy of Neurology (Practice Guideline Update Summary: Corticosteroid Treatment of Duchenne Muscular Dystrophy):



In children with DMD, prednisone should be offered for improving strength (Level B) and pulmonary function (Level B). Prednisone may be offered for improving timed motor function (Level C), reducing the need for scoliosis surgery (Level C), and delaying cardiomyopathy onset by 18 years of age (Level C). Deflazacort may be offered for improving strength and timed motor function and delaying age at loss of ambulation by 1.4–2.5 years (Level C). Deflazacort may be offered for improving pulmonary function, reducing the need for scoliosis surgery, delaying cardiomyopathy onset, and increasing survival at 5–15 years of follow-up (Level C for each). Deflazacort and prednisone may be equivalent in improving motor function (Level C). Prednisone may be associated with greater weight gain in the first years of treatment than deflazacort (Level C). Deflazacort may be associated with a greater risk of cataracts than prednisone (Level C). The preferred dosing regimen of prednisone is 0.75 mg/kg/d (Level B). Over 12 months, prednisone 10 mg/kg/weekend is equally effective (Level B), with no long-term data available. Prednisone 0.75 mg/kg/d is associated with significant risk of weight gain, hirsutism, and cushingoid appearance (Level B).

The Canadian National Health Technology Assessment Agency Review

CADTH, the Canadian national health technology assessment agency, published a review of novel therapies for DMD in June 2017. The review outlines the various approaches to treatment currently available or under investigation:

Corticosteroids and assistive devices remain the mainstay of therapy. Prednisone is recommended first line. Deflazacort, available in Europe and approved in the U.S., may cause less weight gain, but at several orders of magnitude higher cost.

2018 Update

A detailed literature search for new clinical data from 1/1/17 to 5/11/18 and scan of 2016 for registration trial data missing from publication were performed (none was found). Additional data analyses and report from CADTH (2017) added. References updated.



2019 Update

A detailed literature search for new clinical data from 5/1/18 to 2/28/19 found no further evidence requiring change to this policy.

2020 Update

Added background section to policy. Reviewed prescribing information for Exondys 51 (eteplirsen) and Vyondys 53 (golodirsen). No new evidence was identified from prescribing information that required changes to coverage criteria. Reduced from 6 months duration to 3 months duration that the individual has been established on a stable dose of corticosteroids. This change in duration was made by the P&T Committee after review of DMD drugs. Added Viltepso (vitolarsen) to policy for individuals with a confirmed mutation of the DMD gene that is amenable to exon 53 skipping.

2021 Update

Reviewed prescribing information for all drugs listed in policy and checked for updated guidelines on the treatment and management of Duchenne muscular dystrophy. No changes were identified that would impact policy statements.

2022 Update

Reviewed prescribing information for all drugs listed in policy and checked for updated guidelines on the treatment and management of Duchenne muscular dystrophy. No changes were identified that would impact policy statements.

2023 Update

Reviewed prescribing information for all drugs listed in policy. No changes were identified that would impact policy statements. Added coverage criteria for Elevidys for the treatment of ambulatory pediatric individuals aged 4 through 5 years with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the DMD gene.



2024 Update

Reviewed prescribing information for all drugs listed in policy. Added coverage criteria for Agamree (vamorolone) for the treatment of Duchenne muscular dystrophy (DMD) in individuals 2 years of age and older. Updated Agamree (vamorolone) and Emflaza (deflazacort) coverage criteria to include a requirement to try generic deflazacort first. Added coverage criteria for generic deflazacort for the treatment of Duchenne muscular dystrophy (DMD) in individuals 2 years of age and older. Clarified that the Emflaza (deflazacort) and generic deflazacort coverage criteria applies to the oral tablet and oral suspension. Added coverage criteria for Duvyzat (givinostat) for the treatment of certain individuals with Duchenne muscular dystrophy (DMD). Updated the age requirement for Elevidys (delandistrogene moxearovovec-rokl) from 4 to 5 years of age to 4 years or older. Clarified that the use of Elevidys (delandistrogene moxearovovec-rokl) in individuals who are non-ambulatory is considered investigational.

2025 Update

Reviewed prescribing information for all drugs listed in policy. Policy updated to indicate that Site of Service Medical Necessity criteria does not apply to Alaska fully-insured members pursuant to [Alaska HB 226](#) (accessed January 3, 2025). Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Added an exception to the site-of-service requirements for certain individuals receiving treatment for cytokine release syndrome (CRS). Clarified that the Site of Service Medical Necessity criteria can apply to injection drugs.

References

1. Muscular Dystrophy UK. Online database. Available at: <http://www.muscular dystrophyuk.org/progress-in-research/background-information/what-is-exon-skipping-and-how-does-it-work/> Accessed January 6, 2025.
2. Summary of Practice Guidelines for Patients and their Families: Duchenne Muscular Dystrophy: Treatment with Corticosteroids. Available at: <https://www.aan.com/Guidelines/home/GetGuidelineContent/733> Accessed January 6, 2025.
3. The Muscular Dystrophy Association (MDA): For Strength, Independence & Life. Available at: <https://www.mda.org/disease/duchenne-muscular-dystrophy/causes-inheritance> Accessed January 6, 2025.



4. Parent Project Muscular Dystrophy: Leading the Fight to End Duchenne. Available at: http://www.parentprojectmd.org/site/PageServer?pagename=Understand_about Accessed January 6, 2025.
5. Patient: Trusted Medical Information and Support: Health Information: Duchenne Muscular Dystrophy. Available at: <http://patient.info/health/duchenne-muscular-dystrophy-leaflet> Accessed January 6, 2025.
6. Gloss D, MD, MPH; Moxley RT III, MD; Ashwal S, MD; and Oskoui M, MD. Practice Guideline Update Summary: Corticosteroid Treatment of Duchenne Muscular Dystrophy: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* February 2, 2016, vol. 86 no. 5 465-472. Available at: <http://www.neurology.org/content/86/5/465.long#abstract-1> Accessed January 6, 2025.
7. Kinane, Bernard, et al. Long-Term Pulmonary Function in Duchenne Muscular Dystrophy: Comparison of Eteplirsen-Treated Patients to Natural History. *J Neuromuscul Dis.* Dec 2017; doi: 0.3233/JND-170272
8. Exondys 51 Prescribing Information. Sarepta Therapeutics, Cambridge, MA. Revised January 2022.
9. Irwin AN, Herink MC. Eteplirsen for the Treatment of Duchenne Muscular Dystrophy: Quality of Evidence Concerns-an Alternative Viewpoint. *Pharmacotherapy.* 2017 Oct;37(10):e109-e111. doi: 10.1002/phar.1996. Epub 2017 Sep 12.
10. Shawi F, Perras C, Severn M. CADTH Issues in Emerging Health Technologies. 161Emerging Drugs for Duchenne Muscular Dystrophy. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2016-.161. 2017 Jun 01.
11. Aslesh T, Maruyama R, Yokota T. Skipping Multiple Exons to Treat DMD-Promises and Challenges.
12. *Biomedicines.* 2018 Jan 2;6(1). pii: E1. doi: 10.3390/biomedicines6010001. Review. PMID: 29301272
13. Charleston JS, Schnell FJ, Dworzak J, et al. Eteplirsen treatment for Duchenne muscular dystrophy: Exon skipping and dystrophin production. *Neurology.* 2018 May 11. pii: 10.1212/WNL.0000000000005680. doi: 10.1212/WNL.0000000000005680.
14. Kinane TB, Mayer OH, Duda PW, et al. Long-Term Pulmonary Function in Duchenne Muscular Dystrophy: Comparison of Eteplirsen-Treated Patients to Natural History. *J Neuromuscul Dis.* 2018;5(1):47-58. doi: 10.3233/JND-170272.
15. Kinane, Bernard, et al. Long-Term Pulmonary Function in Duchenne Muscular Dystrophy: Comparison of Eteplirsen-Treated Patients to Natural History. *J Neuromuscul Dis.* Dec 2017; doi: 0.3233/JND-170272
16. Irwin AN, Herink MC. Eteplirsen for the Treatment of Duchenne Muscular Dystrophy: Quality of Evidence Concerns-an Alternative Viewpoint. *Pharmacotherapy.* 2017 Oct;37(10):e109-e111. doi: 10.1002/phar.1996. Epub 2017 Sep 12.
17. Amondys 45 Prescribing Information. Sarepta Therapeutics, Cambridge, MA. Revised July 2024.
18. Vyondys 53 Prescribing Information. Sarepta Therapeutics, Cambridge, MA. Revised June 2024.
19. Viltepso Prescribing Information. NS Pharma, Inc., Paramus, NJ. Revised March 2021.
20. Clemens PR, Rao VK, Connolly AM, et al. Safety, Tolerability, and Efficacy of Viltolarsen in Boys with Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping: A Phase 2 Randomized Clinical Trial. *JAMA Neurol.* May 2020. doi:10.1001/jamaneurol.2020.1264
21. Clemens P, Rao V, Connolly A, et al. Dystrophin restoration by exon 53 skipping in patients with Duchenne muscular dystrophy after viltolarsen treatment: phase 2 study update. *Neuromuscular Disorders.* October 2019. doi:10.1016/j.nmd.2019.06.451.
22. 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;9:77-93.
23. Sarepta Therapeutics Announces Positive Expression Results from the Casimersen (SRP-4045) Arm of the ESSENCE Study | Sarepta Therapeutics, Inc. Sarepta Therapeutics, Inc. <https://investorrelations.sarepta.com/news-releases/news-release-details/sarepta-therapeutics-announces-positive-expression-results>. Accessed January 6, 2025.
24. Sarepta Therapeutics. Dose-Titration and Open-label Extension Study of SRP-4045 in Advanced Stage Duchenne Muscular Dystrophy (DMD) Patients. Available from: <https://clinicaltrials.gov/ct2/show/NCT02530905>. Accessed January 6, 2025.
25. Passamano L, Taglia A, Palladino A, et. al. Improvement of survival in Duchenne Muscular Dystrophy: retrospective analysis of 835 patients. *Acta Myologica,* 2012;121-125.



26. Elevidys (delandistrogene moxeparvovec-rokl). [Package Insert]. Cambridge, MA; Sarepta Therapeutics, Inc. Revised August 2024.
27. Agamree (vamorolone). [Package Insert]. Burlington, MA; Santhera Pharmaceuticals (Switzerland) Ltd. Revised June 2024.
28. Duvyzat (givinostat). [Package Insert]. Concord, MA; ITF Therapeutics, LLC. Revised November 2024.

History

Date	Comments
01/01/17	New policy, approved December 13, 2016. Add to Prescription Drug Section.
04/01/17	Annual Review, approved March 14, 2017. Updated criteria based on the P&T Committee's expert recommendation provided at a quarterly P&T meeting.
01/01/18	Coding update, added HCPCS code J1428 (new code effective 1/1/18).
02/01/18	Interim Review, approved January 16, 2018; effective June 1, 2018, Exondys 51 (eteplirsen) becomes subject to review for site of service administration.
02/14/18	Annual Review, approved February 6, 2018. Policy updated with literature review through December 2017. Information added regarding the effect on pulmonary function from 4 year, open-label study. No change to the policy statement. Approved February 13, 2018, to update hospital-based outpatient coverage from 30 days to 90 days.
06/01/18	Minor update: removed note and link to updated policy. Site of Service criteria becomes effective.
08/01/18	Interim Review, approved July 10, 2018. Policy updated including a detailed search for new clinical data from 1/1/17 to present and scan of 2016. Additional data analyses and report from CADTH (2017) added.
09/21/18	Minor update. Added Consideration of Age statements.
11/01/18	Minor update, the Site of Service criteria was updated for clarity.
01/01/19	Minor update. Clarified Consideration of Age information.
04/01/19	Annual Review, approved March 19, 2019. Updated literature search. No changes.
04/01/20	Interim Review, approved March 10, 2020. Title changed from "Exondys 51 (eteplirsen)" to "Pharmacologic Treatment of Duchenne Muscular Dystrophy". Added criteria for Vyondys 53 (golodirsen) for the treatment of DMD in patients amenable to exon 53 skipping. Added HCPCS code J3590. Moved Emflaza (deflazacort) from policy 5.01.605 with identical coverage criteria.
07/01/20	Coding update. Added code J1429. Removed code J3590.
11/01/20	Annual Review, approved October 13, 2020. Added criteria for Viltepso (vitolarsen) for the treatment of DMD in patients amenable to exon 53 skipping. Updated criteria for



Date	Comments
	Exondys 51 (eteplirsen) and Vyondys 53 (golodirsen) reducing from 6 months duration to 3 months duration that the patient has been established on a stable dose of corticosteroids. Added J3590 for Viltepso (vitolarsen).
01/01/21	Coding update, Added HCPCS code C9071.
04/01/21	Coding update. Removed HCPC J3590 as there is a new code for Viltepso (vitolarsen), Added term date to HCPC C9070, added new HCPC code J1427.
05/01/21	Interim Review, approved April 13, 2021. Added criteria for Amondys 45 (casimersen) for the treatment of DMD in patients amenable to exon 45 skipping. Added site of service review for Vyondys 53 (golodirsen) for dates of service on or after August 6, 2021. Added HCPC J3590.
07/01/21	Coding update, Added HCPCS code C9075.
11/01/21	Annual Review, approved October 21, 2021. Added site of service review for Amondys 45 (casimersen) for dates of service on or after February 4, 2022. Coding update, Added HCPCS J1426 and removed HCPCS J3590.
09/01/22	Annual Review, approved August 8, 2022. No changes to policy statements. Removed HCPCS code C9071.
03/01/23	Annual Review, approved February 20, 2023. Added a 1-year re-authorization duration to all drugs listed in policy. Removed terminated HCPC code C9075. Removed effective date from HCPC code J1426. Changed the wording from "patient" to "individual" throughout the policy for standardization.
10/01/23	Interim Review, approved September 12, 2023. Added coverage criteria for Elevidys for the treatment of ambulatory pediatric individuals aged 4 through 5 years with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the DMD gene. Added HCPCS codes C9399 and J3590 for Elevidys.
01/01/24	Coding update. Added new HCPCS code J1413 and removed J3590 and C9399.
02/01/24	Annual Review, approved January 9, 2024. Added coverage criteria for Agamree (vamorolone) for the treatment of Duchenne muscular dystrophy (DMD) in individuals 2 years of age and older.
05/01/24	Interim Review, approved April 9, 2024. Updated Agamree (vamorolone) and Emflaza (deflazacort) coverage criteria to include a requirement to try generic deflazacort first. Added coverage criteria for generic deflazacort for the treatment of Duchenne muscular dystrophy (DMD) in individuals 2 years of age and older.
08/01/24	Interim Review, approved July 9, 2024. Clarified that the Emflaza (deflazacort) and generic deflazacort coverage criteria applies to the oral tablet and oral suspension. Added coverage criteria for Duvyzat (givinostat) for the treatment of certain individuals with Duchenne muscular dystrophy (DMD).
11/01/24	Interim Review, approved October 8, 2024. Updated the age requirement for Elevidys (delandistrogene moxeparvovec-rokl) from 4 to 5 years of age to 4 years or older.



Date	Comments
	Clarified that use of Elevidys (delandistrogene moxeparvovec-rokl) in individuals who are non-ambulatory is considered investigational.
02/01/25	Annual Review, approved January 27, 2025. Policy updated to indicate that Site of Service Medical Necessity criteria does not apply to Alaska fully-insured members; only Medical Necessity criteria for the infusion drug applies pursuant to Alaska HB 226 (link added). Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Added an exception to the site-of-service requirements for certain individuals receiving treatment for cytokine release syndrome (CRS).
07/01/25	Interim Review, approved June 10, 2025. The following policy changes are effective October 3, 2025, following 90-day provider notification. Clarified that the Site of Service Medical Necessity criteria can apply to injection drugs.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2025 Premera All Rights Reserved.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

