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Casimersen

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For Illinois only: Illinois Public Act 103-0458 [Insurance Code 215 ILCS 5/356z.61] (HB3809 Impaired Children) states all group or individual fully insured PPO, HMO, POS plans amended, delivered, issued, or renewed on or after January 1, 2025 shall provide coverage for therapy, diagnostic testing, and equipment necessary to increase quality of life for children who have been clinically or genetically diagnosed with any disease, syndrome, or disorder that includes low tone neuromuscular impairment, neurological impairment, or cognitive impairment.

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug

approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Amondys 45™ (casimersen) for the treatment of Duchenne muscular dystrophy **is considered not medically necessary** as a clinical benefit has not been established.

Amondys 45™ (casimersen) for the treatment of all other indications **is considered experimental, investigational and/or unproven.**

Policy Guidelines

None.

Description

Background

Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is an X-linked, recessive disorder that occurs in approximately 1 in 3500 to 5000 males. (1) It primarily affects males. However, a small number of females are also affected, but they are usually asymptomatic. Even when symptomatic, most females typically only present with a mild form of the disease. According to United States (U.S.) epidemiologic data, the first signs or symptoms of DMD are usually noted at a mean age of 2.5 years (range, 0.2-1 years), and the mean age at definitive diagnosis is 4.9 years (range, 0.3-8.8 years). (2) Symptoms include motor difficulties such as difficulty running, jumping, and walking upstairs, along with an unusual waddling gait. Some improvement in symptoms may be seen from 3 to 6 years of age, though gradual deterioration resumes, and most patients lose ambulation by age 12 and require noninvasive ventilation by late teenage years. Patients progress from needing noninvasive ventilation only during night sleeping, followed by noninvasive ventilation during day and night sleeping, and then noninvasive ventilation during day and night over the course of 5 to 10 years.

DMD occurs as a result of variant(s) in the gene responsible for producing dystrophin, a cohesive protein that is essential for maintaining muscle support and strength. *Duchenne muscular dystrophy* is the longest known human gene, and several variants can cause DMD. Most deletion variants disrupt the translational reading frame in the dystrophin messenger ribonucleic acid (RNA) resulting in an unstable, nonfunctional dystrophin molecule. As a result, there is progressive muscle degeneration leading to loss of independent ambulation, as well as other complications, including respiratory and cardiac complications. (3) Genetic testing is required to determine the specific *Duchenne muscular dystrophy* gene variant(s*)* for a definitive diagnosis, even when the absence of dystrophin protein expression has been confirmed by muscle biopsy. There are over 4700 variants in the Leiden DMD mutation database, and the most common variants are concentrated between exons 45 and 53.

Regulatory Status

In February 2021, casimersen (Amondys 45™; Sarepta Therapeutics) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of DMD in patients who have a confirmed mutation of the *Duchenne muscular dystrophy* gene that is amenable to exon 45 skipping. This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with casimersen.

The FDA, under the accelerated approval regulations (21 CFR 314.510), requires that Sarepta verify the clinical benefit of casimersen by completing Study 4045-301 (Essence), A Double-Blind, Placebo-Controlled, Multicenter Study with an Open-Label Extension to Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in participants with Duchenne Muscular Dystrophy. The study includes a randomized, double-blind, placebo-controlled period of 96 weeks and concludes after an open label extension period to 144 weeks. The primary endpoint will be the 6-minute walk test. The expected date of trial completion is April 2024 and final report submission to the FDA by October 2024.

Rationale

This medical policy was created in 2021 and was based on review of available evidence in the scientific literature. The most recent literature update was performed through December 16, 2023.

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function−including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Casimersen for Treatment of Duchenne Muscular Dystrophy

Clinical Context and Therapy Purpose

The purpose of casimersen in individuals who have a confirmed variant of the *Duchenne muscular dystrophy* gene that is amenable to specific exon skipping, is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this medical policy is: Does the use of casimersen in individuals with a *Duchenne muscular dystrophy* gene variant that is amenable to specific exon skipping improve the net health outcome compared with continued medical management?

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is patients with a confirmed variant of the *Duchenne muscular dystrophy* gene that is amenable to specific exon skipping.

Interventions

The therapy being considered is the antisense oligonucleotide, casimersen. Phosphorodiamidate morpholino oligomers are stable oligonucleotide analogues that selectively bind to RNA to alter gene expression. In the case of casimersen, the phosphorodiamidate morpholino oligomer binds to exon 45 of the dystrophin pre-messenger RNA causing the exon to be skipped and prevents that part of the code from being read during messenger RNA processing, thereby partially repairing the mutated reading frame in the messenger RNA coding sequence. As a result, casimersen enables the production of an internally truncated, yet functional, dystrophin protein.

Comparators

The following practice is currently being used to treat patients with a confirmed variant of the *Duchenne muscular dystrophy* gene: standard multidisciplinary care including pharmacotherapy. Pharmacotherapy primarily involves corticosteroids (mainly prednisone or deflazacort) for all individuals regardless of the genetic variant. Treatment is initiated once

patients reach a plateau of motor skill development, generally at ages 4 to 6 years, but before the onset of motor decline. The goal of corticosteroid therapy is to preserve ambulation and minimize respiratory, cardiac, and orthopedic complications. In addition, muscle weakness and pain, cardiac, pulmonary, orthopedic, and endocrine symptoms should be managed. (1)

Outcomes

The general outcomes of interest are a change in disease status, functional outcomes, quality of life, treatment-related mortality, and treatment-related morbidity. See Table 1 for the description and relevance of specific outcome measures considered in this policy.

As per the U.S. Food and Drug Administration (FDA) guidance document for developing drugs for the treatment of dystrophinopathies, the FDA has no defined set of required or recommended clinical outcome measures to be used in clinical studies. The guidance states that manufacturers should propose and, if necessary, develop endpoints that can validly and reliably assess patients with a wide spectrum of symptoms and disease stages. Further, it states, "The sponsor should include an assessment of multiple efficacy endpoints, when feasible, to characterize the breadth of effects on dystrophin-related pathologies, including skeletal, respiratory, and cardiac muscle function, even if the primary endpoint is only 1 of these measures." (4)

Table 1. Health Outcome Measures That May Be Relevant to Muscular Dystrophinopathies

Outcome Measure	Description	Scale	Clinically Meaningful Difference/Comment
Griffiths scale of mental development	Comprehensive, child-friendly developmental measure for continuous use from birth to 6 years (72 months).	Consists of 2 sets of scales, 1 for each age group 0-2 years and 2-8 years.	Although used in Duchenne muscular dystrophy, this is a non-specific measure and its appropriateness to measure clinical efficacy for Duchenne muscular dystrophy has not been established.
Bayley scales of infant and toddler development (Third edition)	Designed to assess developmental functioning from 1 month to 42 months of age. Covers 5 domains: cognitive, language, motor, adaptive, and social-emotional development.	Composite scores are derived for cognitive, language, and motor development and scaled to a metric, with a mean of 100, standard deviation of 15, and range of 40 to 160.	Although used in Duchenne muscular dystrophy, this is a non-specific measure and its appropriateness to measure clinical efficacy for Duchenne muscular

			dystrophy has not been established.
North Star Ambulatory Assessment (NSAA) or an age appropriate modified NSAA	Measures functional motor abilities. Appropriate for ambulatory children ages ≥ 3 years of age with Duchenne muscular dystrophy.	17-item scale that grades each activity from 0 (unable to achieve independently) to 2 (normal- no obvious modification of activity). Scores can range from 0 to 34. Higher scores indicate improvement. Also includes recording timed items such as the 10-meter timed walk/run test and time to rise from the floor (Gower's test). These times are not included in the global score.	Not reported.
6-minute walk test (6MWT) or shorter versions such as the 2-minute walk test	Measures strength and endurance, can be appropriate for patients as young as 5-6 years of age. Performance may increase with time in very young patients whereas performance tends to worsen with time in older patients. Floor effect of losing ambulation in older patients with more advanced disease and analyses of change in 6MWT can be strongly influenced by the inclusion or exclusion of patients who lose	Assesses distance walked in 6 minutes.	Estimates of minimum clinically important difference for Duchenne muscular dystrophy patients of a change of 30 meters have been reported. (5, 6) Interpretation of 6MWT results is limited by the variability in testing procedures and patient motivation.

	ambulation during the trial; such patients contribute zero values.		
Myometric assessments	Appropriate to measure increase or preservation of muscle strength, and it can be used to provide reliable measurements in children ages 5 years and older.		Clinical meaningfulness of differences in muscle strength should be supported by the magnitude of the effect observed or by the demonstration of a drug effect on an appropriate functional measure.
Specific clinical respiratory outcomes	Nocturnal desaturation, aspiration pneumonia, and progression to mechanically assisted ventilation.	Varied outcome measure (dichotomous or continuous).	Clinical meaningfulness of differences should be supported by the magnitude of the effect observed or by the demonstration of a drug effect on an appropriate functional measure.
Biomarker (such as dystrophin)	Deficiency of functional dystrophin appears to be the proximate cause of the symptomatic and functional consequences of dystrophinopathies, justifying particular interest in dystrophin as a biomarker and as a potential surrogate endpoint for accelerated approval.	Dystrophin levels are measured in muscle fibers by immunohistochemical analysis to detect the presence or absence of dystrophin regardless of the actual quantity of dystrophin present while Western blot analysis quantifies the amount of dystrophin in the muscle tissue sample.	Dystrophin expression can only be viewed as supportive of the proof of principle. It is currently uncertain how predictive of sustained functional improvement the detected dystrophin level could be, and what levels may be required for a meaningful clinical improvement in Duchenne patients to be registered. Further, dystrophin produced by

			casimersen is an internally shortened protein and the clinical effect of the truncated dystrophin is still not fully known.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

The clinical development program of casimersen for individuals with Duchenne muscular dystrophy includes a single, ongoing, double-blind, placebo-controlled, multicenter study called ESSENCE, summarized in Table 2.

Table 2. Summary of the Clinical Development Program for Casimersen

Trial	NCT	Phase	Description	N	Design	Status
ESSENCE (4045-301) (8)	NCT02500381	2	Efficacy and safety of casimersen	111	DBRCT (part 1) and open-label (part 2)	Ongoing (unpublished)

DBRCT: double-blind randomized controlled trial; NCT: national clinical trial.

Pivotal Trial

Trial characteristics and results of the pivotal ESSENCE trial as reported in the FDA prescribing label are summarized in Tables 3 and 4, respectively. The ESSENCE trial was initiated in 2016 with a planned enrollment of 111 participants. The interim analysis reported data from 43 participants who were randomized to receive a once-weekly intravenous infusion of casimersen dosed at 30 mg/kg (n=27) or placebo (n=16). Interim efficacy was assessed based on change from baseline in the dystrophin protein level (measured as % of the dystrophin level in healthy subjects, i.e., % of normal) at week 48. Safety and pharmacokinetic parameters of a subset of 12 participants have been published but are not reported here. (7) As with other FDA approved antisense oligonucleotides (such as eteplirsen, golodirsen, and viltolarsen), no specific safety issues were observed in the limited number of participants who were evaluated in the ESSENCE trial. Most reported treatment emergent adverse events were mild in severity; 2 were

related to treatment, and no participants discontinued study drug or reduced dosage due to adverse events. No clinically significant laboratory abnormalities or worsening in electrocardiograms and echocardiograms were noted. (8)

Table 3. Summary of Trial Characteristics of a Key Randomized Trial of Casimersen

					Description of Interventions	
Study	**Countries**	**Sites**	**Dates**	**Participants**	**Active**	**Comparator**
ESSENCE (8)	Multi-national	66	2016-present	• Males aged 7 to 13 years with DMD and confirmed genetic mutation amenable to exon 45 skipping • Stable pulmonary function • Stable dose of corticosteroids for ≥6 months • Major exclusions[a] • Primary endpoint: Change in 6MWT from baseline to week 96 • Secondary endpoints: Change in 6MWT at week 144, change in dystrophin protein and dystrophin intensity levels at week 48 or 96, and ability to rise independently	• Part 1 (96 weeks): Casimersen 30 mg/kg (n = not reported) • Part 2 (up to 144 weeks): Casimersen 30 mg/kg (n = not reported)	Part 1 (96 weeks): Placebo (n=not reported)

				from the floor, time to loss of ambulation, change in NSAA scores, and change in FVC% predicted at week 96 and 144		

6MWT: 6-minute walk distance; DMD: Duchenne muscular dystrophy; FVC: forced vital capacity; NSAA: The North Star Ambulatory Assessment

[a] Treatment with gene therapy at any time; previous treatment with DMD experimental treatments within 24 weeks prior to week 1, current or previous treatment with any other experimental treatment (other than deflazacort) within 12 weeks prior to week 1, major surgery within 3 months prior to week 1, presence of other clinically significant illness.

Table 4. Summary of Interim Efficacy Results of a Key Randomized Trial of Casimersen

Study	Placebo	Casimersen
ESSENCE (8)		
N	16	27
Baseline mean dystrophin levels (% of normal)	0.54 (±0.79)	0.93 (±1.67)
Week 48 mean dystrophin levels (% of normal)	0.76 (±1.15)	1.74 (±1.97)
Change from baseline mean	0.22 (±0.49)	0.81 (±0.70)
P-value change from baseline to week 48	<.09	<.001
Between group difference	0.59 (p=.004)	

Tables 5 and 6 display notable relevance and design and conduct limitations identified in the study.

Table 5. Study Relevance Limitations

Study; Trial	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
ESSENCE (8)				2. Reported outcome was a physiologic measure (dystrophin level) and correlation with clinical benefit is	

				unknown 6. Clinical significant difference not supported	

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 6. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
ESSENCE (8)					1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference	

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing

data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

Section Summary: Casimersen

For individuals with a confirmed variant of the *Duchenne muscular dystrophy* gene that is amenable to exon 45 skipping who receive casimersen, the evidence includes a single double-blind, placebo-controlled phase 3 trial. An interim analysis conducted at week 48 with data from 46 participants with exon 45 skipping (casimersen=27 and placebo=16) is available. Compared to those who received placebo, participants who received casimersen demonstrated a statistically significant increase in dystrophin production by 0.59% at week 48 as measured by Western blot. The mean change from baseline to week 48 in dystrophin production was 0.81% versus 0.22% (p=.004) in the casimersen versus placebo arms respectively. There are no satisfactory data clearly establishing the effectiveness of the truncated dystrophin. Further, the minimum beneficial amount of dystrophin expression to be translated into a clinical benefit has yet to be established. In the absence of clinical data convincingly demonstrating a clinical effect, it cannot be concluded that the amount of dystrophin expressed with casimersen will translate into a clinical benefit to patients.

Summary of Evidence

The clinical benefit of Amondys 45™ (casimersen) for the treatment for Duchenne muscular dystrophy (DMD) has not been demonstrated. The establishment of a clinical benefit, including improvement in motor and pulmonary function, in longer-term studies is still needed. In addition, the Food and Drug Administration (FDA) prescribing information concluded, "Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials."

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 7.

Table 7. Summary of Key Trials

NCT Number	Trial name	Planned Enrollment	Completion Date
NCT04179409	A 48-Week, Open Label, Study to Evaluate the Efficacy and Safety of Casimersen, Eteplirsen and Golodirsen in Subjects With Duchenne Muscular Dystrophy Carrying Eligible DMD Duplications	3	Sep 2023 (completed)

NCT02500381	Study of SRP-4045 and SRP-4053 in DMD Patients (ESSENCE)	229	Oct 2025
NCT03532542	An Extension Study to Evaluate Casimersen or Golodirsen in Patients with Duchenne Muscular Dystrophy	260	Aug 2026

NCT: national clinical trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	C9399, J1426, J3490, J3590

*Current Procedural Terminology (CPT®) ©2022 American Medical Association: Chicago, IL.

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randomized, double-blind, placebo-controlled, dose-titration trial. Muscle Nerve. Sep 2021; 64(3):285-292. PMID 34105177
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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
02/01/2024	Document updated with literature review. Coverage unchanged. Add/updated references 2 and 4-8.
10/15/2022	Reviewed. No changes.
09/15/2021	New medical document. Amondys 45™ (casimersen) for the treatment of Duchenne muscular dystrophy is considered not medically necessary as a clinical benefit has not been established. Amondys 45™ (casimersen) for the treatment of all other indications is considered experimental, investigational and/or unproven.