Original Effective Date: 04/2021
Current Effective Date: 05/31/2024
Last P&T Approval/Version: 04/24/2024
Next Review Due By: 04/2025
Policy Number: C21153-A

Amondys 45 (casimersen) NC

PRODUCTS AFFECTED

Amondys 45 (casimersen)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Duchenne muscular dystrophy (DMD)

REQUIRED MEDICAL INFORMATION:
Amondys 45 (casimersen) is considered experimental and not medically necessary for all indications, including but not limited to Duchenne muscular dystrophy (DMD), due to insufficient evidence of therapeutic value since clinical benefit has not been established. Data from clinical studies of casimersen in a small number of people with DMD have demonstrated a consistent safety and tolerability profile. However, the pivotal trials were not designed to evaluate long-term safety and a clinical benefit of Amondys 45 has not been established. The prescribing information for Amondys 45 states that a clinical benefit has not been established. Due to the lack of clinical efficacy data, approval is not recommended for Amondys 45.

Molina Healthcare will continue to evaluate and update this policy as relevant clinical evidence becomes available to determine whether Amondys 45 (casimersen) provides clear clinical benefit or slows progression of the disease.

CONTINUATION OF THERAPY:
NA

DURATION OF APPROVAL:
NA

PRESCRIBER REQUIREMENTS:
NA

AGE RESTRICTIONS:
NA

QUANTITY:
NA

PLACE OF ADMINISTRATION:
NA

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Intravenous infusion

DRUG CLASS:
Muscular Dystrophy – Gene Therapy Agents

FDA-APPROVED USES:
Indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping.

This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with Amondys 45. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Muscular dystrophy includes a group of genetic disorders that cause muscle weakness and progressive disability. Duchenne muscular dystrophy (DMD) is the most common and progresses most rapidly.

Duchenne muscular dystrophy (DMD)

- A rare genetic disorder characterized by progressive muscle deterioration and weakness
- An X-chromosome-linked disease recessive disorder caused by mutations (mainly deletions) in the dystrophin gene that lead to an absence or defect in the dystrophin protein, dystrophin is essential for maintenance of myocyte integrity and helps keep muscle cells intact
- As males have only one X chromosome, and therefore one single copy of the dystrophin gene, they have a much higher probability of developing DMD. A small number of females are also affected but remain asymptomatic and only rarely present with a mild form of the disease.
- It is the most common type of muscular dystrophy. DMD is caused by an absence of dystrophin, a protein that helps keep muscle cells intact.
- In United States, estimated prevalence of DMD is 1.51-2.05 per 10,000 boys aged 5-9 years
- Associated with complete inability to produce functional dystrophin protein
- Affected children with DMD typically develop symptoms in early childhood around 3-5 years old, experiencing progressive muscle weakness and deterioration. Patients with DMD progressively lose the ability to perform activities independently and usually become non- ambulatory by their early teenage years and require the use of a wheelchair.
- As the disease progresses, life-threatening heart and respiratory conditions can occur. Patients typically succumb to the disease in their 20s or 30s; however, disease severity and life expectancy vary.
- In absence of treatment, the patient experiences:
    - wheelchair dependence before age 13 years
    - death occurs by, or around, age 20 years

Prognosis of DMD

- Death occurs around age 20 in absence of treatment and is usually due to cardiac or respiratory failure
- Disease progression in patients with DMD
    - Scoliosis is frequent after loss of ambulation
    - Risk for cardiomyopathy increases with age in absence of ventilatory intervention

Treatment Overview: Pharmacologic Agents/Conventional Therapy

There is no curative therapy, but management of disease manifestations can prolong survival and improve quality of life. A multidisciplinary team is required for management of patient with DMD and treatment options for DMD predominantly focus on management of symptoms and secondary complications.

Goals of management for DMD include:

- Preserve strength, ambulation, and ventilatory and cardiac function
- Minimize of steroid complications where applicable
- Prevent and treat complications including contractures, scoliosis, ventilatory function impairment or failure, and cardiomyopathy
- Determine and arrange appropriate school environment and manage family stressors

Other pharmacologic therapies for DMD are primarily aimed at the management of comorbidities such as cardiomyopathy, osteoporosis, pain management, and respiratory failure. These treatment options include angiotensin-converting-enzyme (ACE) inhibitors, beta-blockers, calcium and vitamin D supplements, muscle relaxants, and non-steroidal anti-inflammatory drugs.

◆ Corticosteroids

- DMD Care Considerations Working Group consensus guidelines urge consideration of glucocorticoid therapy (prednisone or deflazacort) for all patients with DMD (optimal dose ranges not established)[A]
    - Goal in the ambulatory child is to preserve ambulation and minimize later respiratory, cardiac, and orthopedic complications
- Goal of continuing glucocorticoid therapy after loss of ambulation is to preserve upper limb

strength, reduce scoliosis progression, and delay declines in respiratory and cardiac function Generally used to preserve ambulation and minimize complications in patients with DMD
- In ambulatory patients, recommended if motor skills have plateaued or begun to decline
- In non-ambulatory patients, glucocorticoids often continued if already started while ambulatory, but limited evidence regarding starting glucocorticoids
- Daily dosing preferred over alternative regimens (alternate day, high-dose weekend, or 10-day cycles)
- Monitor and manage side effects associated with chronic steroid therapy

Clinical Evidence
The FDA approved Amondys 45 based on interim efficacy at Week 48 of the Phase 3 ESSENCE trial, which is still ongoing and expected to conclude in 2024 as the confirmatory trial for Amondys 45 and Vyondys 53.

Phase 3 ESSENCE trial (NCT02500381)- global, randomized, double-blind, placebo-controlled; also known as Study 4045-301), The study will enroll 222 boys from 7 to 13 years of age with genotypically confirmed DMD and 6MWT ≥ 300 m and ≤ 450 m. The primary endpoint is the change from baseline to Week 96 in 6MWT. Following the 96- week double-blind period, all patients began or are to begin an additional 48 week open-label treatment period. Interim efficacy was assessed based on change from baseline in the dystrophin protein level (measured as % of the dystrophin level in healthy subjects, i.e., % of normal determined by Western Blot) at Week 48

Study Population
Interim results from 43 evaluable male patients with Duchenne muscular disease (DMD) who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping were included in an interim analysis and are presented in this table.
- Patients who provided muscle biopsy data had a median age of 9 years (range, 7–13 years) and 86% were White.
- Key inclusion criteria: Patients were required to have been on a stable dose of oral corticosteroids for at least 24 weeks prior to dosing with Amondys 45 or placebo

Interventions 43 male patients 7 to 13 years of age were randomized 2:1 to receive one of the following every
week for up to 96 weeks, although interim results at 48 weeks were reviewed for the FDA accelerated approval:
- Placebo (n = 16)
- Amondys 45 (30 mg/kg/week) via IV infusion (n = 27)

Following the 96-week double-blind period, all patients began or will begin an additional 48-week open-label treatment period

Endpoints
- Interim efficacy was assessed based on a change from baseline in the dystrophin protein level(measured as percentage of the dystrophin level in healthy subjects, i.e. percentage of normal) at Week 48.
- Interim results at Week 48:

Dystrophin Levels (% of Normal) at Baseline and at Week 48 from Muscle Biopsy: Interim Results

	Placebo	Amondys 45
Dystrophin by Sarepta Western blot	n = 16	n = 27
Baseline Mean (SD)	0.54 (0.79)	0.93 (1.67)
Week 48 Mean (SD)	0.76 (1.15)	1.74 (1.97)
Change from Baseline Mean (SD)	0.22 (0.49)	0.81 (0.70)
P Value Change from Baseline to Week 48	0.09	<0.001
Between-Group Mean Difference 0.59		
P Value Between Groups 0.004		

Efficacy and Safety Results

- Patients who received Amondys 45 showed a significantly greater increase in dystrophin protein levels from baseline to Week 48 of treatment compared to those who received placebo.
- Although kidney toxicity was not observed in the Amondys 45 clinical studies, kidney toxicity was observed in the nonclinical studies. Kidney toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides. Kidney function should be monitored in patients taking Amondys 45.
- The most common side effects observed in DMD patients treated with Amondys 45 were upper respiratory tract infections, cough, fever, headache, joint pain, and throat pain.
- Other adverse reactions that occurred in at least 10% of patients treated with Amondys 45, and that were reported at a rate at least 5% more frequently in the Amondys 45 group than in the placebo group, were ear pain, nausea, ear infection, posttraumatic pain, and dizziness and light- headedness. Estimated primary completion date for ESSENCE is May 2022 with estimated study completion in May 2023. An additional open label trial is being done (NCT03532542) that requires individuals have completed a clinical trial evaluating either casimersen or golodirsen, per protocol, with an estimated completion date of August 2026. Currently, there are no published data or trial results available for casimersen

On August 25, 2020, the Food and Drug Administration (FDA) accepted the New Drug Application (NDA) under the priority review for casimersen for patients with DMD amenable to skipping exon 45. The FDA also gave conditional approval of Amondys-45 as the brand name for casimersen. Casimersen is a phosphordiamidate morpholino oligomer (PMO) that is engineered to treat patients with Duchenne muscular dystrophy (DMD) who have genetic mutations that are amenable to skipping exon 45 of the dystrophin gene. Casimersen is designed to bind to exon 45 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with generic mutations that are amenable to exon 45 skipping. Exon skipping is intended to allow for production of an internally truncated dystrophin protein.

The FDA instituted its Accelerated Approval Program to allow for earlier approval of drugs that treat serious conditions, and that fill an unmet medical need based on a surrogate endpoint. A surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit but is not itself a measure of clinical benefit. The use of a surrogate endpoint can considerably shorten the time required prior to receiving FDA approval.

The NDA included data from the casimersen arm of the ESSENCE study. The ESSENCE study is a double-blind, placebo-controlled, multi-center study to evaluate the efficacy and safety of SRP- 4045 [Amondys 45 (casimersen)] and SRP-4053 [Vyondys 53 (golodirsen)]. Eligible patients with out-of- frame deletion mutations amenable to exon 45 or 53 skipping will be randomized to receive once weekly intravenous infusions of 30 mg/kg SRP-4045 or 30 mg/kg SRP-4053 respectively (combined- active group) or placebo for up to 96 weeks (the placebo-controlled period of the trial). This will be followed by an open label extension period in which all patients will receive open-label active treatment for 48 weeks (up to week 144 of study).

The primary outcome measure was change in baseline in the total distance walked during 6-minute walk test (6MWT) at Week96. Secondary outcome measures included:

- Change from baseline in the 6MWT at Week 144
- Change from baseline in dystrophin protein levels determined by Western Blot at Weeks 48 or 96
- Change from baseline in dystrophin intensity levels determined by immunohistochemistry at Weeks 48 or 96
- Ability to rise independently from the floor
- Time to loss of ambulation
- Change from baseline in the North Star Ambulatory Assessment (NSSA) total score at Week 96 and Week 144
- Change from baseline in Forced Vital Capacity Percent (FVC%) Predicted at Week 96 and Week 144

Clinical efficacy will be assessed at regularly scheduled study visits, including functional tests such as the 6MWT. All patients will undergo a muscle biopsy at baseline and a second muscle biopsy either at Week 48 or Week 96.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Amondys 45 (casimersen) are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. Contraindications to Amondys 45 (casimersen) include: hypersensitivity to casimersen or to any of the inactive ingredients. Instances of hypersensitivity, including angioedema and anaphylaxis, have occurred in patients receiving Amondys 45.

OTHER SPECIAL CONSIDERATIONS:
NA

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
N/A	

AVAILABLE DOSAGE FORMS:
Amondys 45 SOLN 100MG/2ML single-dose vial

REFERENCES

1. Amondys 45 (casimersen) [package insert]. Cambridge, MA: Sarepta Therapeutics, Inc, March 2023.
2. Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 3: primary care, emergency management, psychosocial care, and transitions of care across the lifespan. Lancet Neurol. 2018;17(5):445-455. doi:10.1016/S1474- 4422(18)30026-7
3. Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopedic management. Lancet Neurol. 2018;17(4):347-361. doi:10.1016/S1474-4422(18)30025-5
4. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. Lancet Neurol. 2018;17(3):251-267.doi: 10.1016/S1474-4422(18)30024.
5. American Academy of Neurology. Evidence-Based Guideline Summary: Evaluation, Diagnosis, and Management of Congenital Muscular Dystrophy. Published March 2015. Accessed March 4, 2021. https://www.aan.com/Guidelines/home/GuidelineDetail/683
6. National Institutes of Health, Genetic and Rare Diseases Information Center. Duchenne muscular dystrophy. Updated November 2, 2020. Accessed March 4, 2021. https://rarediseases.info.nih.gov/diseases/6291/duchenne-musculardystrophy
7. Exondys 51 (eteplirsen) [package insert]. Cambridge, MA: Sarepta Therapeutics, Inc, January 2022.
8. Vyondys 53 [package insert]. Cambridge, MA: Sarepta Therapeutics, Inc, February2021.
9. Viltepso [package insert]. Paramus NJ: NS Pharma, Inc, August 2020.
10. Study of SRP-4045 and SRP-4053 in DMD Patients (ESSENCE) https://clinicaltrials.gov/ct2/show/NCT02500381?term=golodirsen&cond=Duchenne+Muscular+Dystrophy

&rank=3.

11. Gloss, D., Moxley, R. T., Ashwal, S., & Oskoui, M. (2016). Practice guideline update summary: Corticosteroid treatment of duchenne muscular dystrophy. Neurology, 86(5), 465-472. doi:10.1212/wnl.0000000000002337

SUMMARY OF REVIEW/REVISIONS	DATE
ANNUAL REVIEW COMPLETED- No coverage criteria changes with this annual review.	Q2 2024
REVISION- Notable revisions: Required Medical Information FDA Approved Uses Contraindications/Exclusions/Discontinuation HCPCS Code Description Available Dosage Forms References	Q2 2023
ANNUAL REVIEW COMPLETED- No coverage criteria changes with this annual review.	Q2 2022
Q2 2022 Established tracking in new format	Historical changes on file