Amondys 45 (casimersen)-MNR
Policy Number: Pending

CRITERIA EFFECTIVE DATES:

ORIGINAL EFFECTIVE DATE	LAST REVIEWED DATE	NEXT REVIEW DUE BY OR BEFORE
04/2021	04/28/2021	04/26/2022
J CODE	**TYPE OF CRITERIA**	**LAST P&T APPROVAL/VERSION**
J3490-Unclassified drugs	RxPA	Q2 2021 20210428

PRODUCTS AFFECTED:
Amondys 45 (casimersen)

DRUG CLASS:
Muscular Dystrophy Agents

ROUTE OF ADMINISTRATION:
Intravenous infusion

PLACE OF SERVICE:
Specialty Pharmacy or Buy and Bill
The recommendation is that medications in this policy will be for medical benefit coverage and the IV infusion products administered in a place of service that is a non-hospital facility-based location (i.e., home infusion provider, provider's office, free-standing ambulatory infusion center) unless the therapy/member meets the Site of Care exceptions.

AVAILABLE DOSAGE FORMS:
Casimersen IV Solution: Single-dose vials containing 100 mg/2 mL (50 mg/mL)

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

COVERAGE CRITERIA: INITIAL AUTHORIZATION

DIAGNOSIS:
Duchenne muscular dystrophy

REQUIRED MEDICAL INFORMATION:
A. DUCHENNE MUSCULAR DYSTROPHY(DMD):
1. Documentation of ALL of the following criteria are required.
   May include chart notes from the member's medical records, relevant labs and/or tests, and other relevant clinical information supporting the diagnosis*

(a)Diagnosis of Duchenne muscular dystrophy (DMD) with mutation amenable to exon 45 skipping confirmed by genetic testing
NOTE: Lab results from genetic testing is required for authorization review. Members who do not have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping will not be authorized.
AND
(b) Documentation that member is ambulatory as evidenced by ONE the following completed in the previous 30 days: 6-minute walk test (6MWT) ≥300 meters while walking independently without assistance or devices (without side-by-side assist, cane, walker, wheelchair, etc.) OR North Star Ambulatory Assessment (NSAA) score >17 OR achieved rise time (Gower's test) <7 seconds
NOTE: Coverage will not be authorized for Members who are wheelchair dependent
AND
(c) Member's weight (in kilograms) and date weight was recorded (weight must be dated no more than 30 days before the request date)
AND
(d) Recent clinical progress and medical records or chart notes relevant to member's condition
AND
(e) Member is currently stable on an oral corticosteroid regimen for at least 6 months, unless contraindicated or member has experienced clinically significant adverse effects.
AND
(f) ONE (1) or more of the following measurable evaluations to assess physical function or the rate of disease progression (not an all-inclusive list). Evaluation must be within the past 30 days: (i) Dystrophin level, (ii) Brooke Upper Extremity Scale, (iii) Forced Vital Capacity assessment
NOTE: The same assessment should be used in the follow-up evaluation at 3 months and every 6 months for re-authorization of continuation of therapy. If the initial assessment tool is not appropriate (i.e. due to change in member's status or age range of the assessment), submit the rationale for change in assessment tool.

DURATION OF APPROVAL:
Initial authorization: 3 months, Continuation of therapy: 6 months

QUANTITY: 30 mg/kg administered once weekly as a 35 to 60-minute intravenous (IV) infusion,

PRESCRIBER REQUIREMENTS:
Prescribed by, or in consultation with, a board-certified physician who specializes in treatment of Duchenne muscular dystrophy in one of the following specialties: neurology, orthopedic, physical medicine and rehabilitation, neuromuscular medicine, or neurodevelopmental disabilities. Submit consultation notes if applicable. NOTE: Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually

AGE RESTRICTIONS:
7 years of age or older

CONTINUATION OF THERAPY:
A. DUCHENNE MUSCULAR DYSTROPHY(DMD):
1. Adherence to therapy at least 85% of the time as confirmed by Prescriber or member's claims history
NOTE: Therapy may be discontinued due to poor adherence upon recommendation of the Molina Medical Director when adherence < 85% has been demonstrated in at least two months during thecourse of therapy
AND

2. Documentation of absence of unacceptable adverse effects or complications from Amondys 45 (casimersen) including: severe infusion-related reactions, interference with automated platelet counts (platelet clumping)
   AND
3. Documentation of positive response to therapy, defined as member remaining ambulatory, as evidenced by ALL of the following evaluations completed within the past 30 days:
   (a) Results of 6-Minute Walk Time (6MWT), while walking independently without assistance or devices (without side-by-side assist, cane, walker, wheelchair, etc.) OR North Star Ambulatory Assessment (NSAA) score >17 OR achieved rise time (Gower's test) <7 seconds
   NOTE: Coverage will not be authorized for Members who are wheelchair dependent.
   AND
   (b) ONE (1) or more of the following measurable evaluations to assess physical function or the rate of disease progression (not an all-inclusive list). Evaluation must be within the past 30 days.
      i. Increase in dystrophin level†, OR
      ii. Brooke Upper Extremity Scale, OR
      iii. Respiratory parameters: Forced Vital Capacity (FVC %) predicted and peak cough flow
   NOTE: The same assessment should be used in the follow-up evaluation at 6 months for re-authorization of continuation of therapy. If the initial assessment tool is not appropriate (i.e. due to change in member's status or age range of the assessment), submit the rationale for change in assessment tool.
   AND
4. Member continues to receive concurrent corticosteroids, unless contraindicated or intolerant (severe adverse reactions)

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Amondys 45 (casimersen)-are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

Authorization will not be granted if ANY of the following conditions apply:
- Member is wheelchair dependent,
- Requested dose and frequency is not in accordance with FDA-approved labeling, nationally recognized compendia, and/or evidence-based practice guidelines
- Non-FDA approved indications

OTHER SPECIAL CONSIDERATIONS:
None

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.

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.

REFERENCES:

1. Amondys 45 [package insert]. Cambridge, MA: Sarepta Therapeutics, Inc, February 2021.
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 orthopaedic 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 [package insert]. Cambridge, MA: Sarepta Therapeutics, Inc, July 2020.
8. Vyondys 53 [package insert]. Cambridge, MA: Sarepta Therapeutics, Inc, February 2021.
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.