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Policy Number: C28336-A

Duvyzat (givinostat)

PRODUCTS AFFECTED

Duvyzat (givinostat)

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:
This clinical policy is consistent with the standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered, and formulary preferencing. Coverage will be determined on a case-by-case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member-specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. DUCHENNE MUSCULAR DYSTROPHY (DMD):
   1. Documented diagnosis of Duchenne muscular dystrophy (DMD) [DOCUMENTATION REQUIRED]
      AND
   2. Documentation of baseline evaluation of physical function as documented by BOTH of the

following evaluations completed in the past 30 days [DOCUMENTATION REQUIRED]:

a. Documentation that member is ambulatory as evidenced by ONE of the following:
- 6-minute Walk Test (6MWT) ≥ 300 meters while walking independently without assistance or devices (without side-by-side assist, cane, walker, wheelchair, etc.)
- North Star Ambulatory Assessment (NSAA) score > 17
- Achieved rise time (Gower's test) < 7 seconds
- 4-stair climb (4SC)
- time to walk/run 10 meters (10MWT)

AND

b. Documentation of ONE or more of the following measurable evaluations to assess physical function or the rate of disease progression (not an all-inclusive list):
- Dystrophin level
- Brooke Upper Extremity Scale
- Forced Vital Capacity assessment

NOTE: The same assessment should be used in the follow-up evaluation for re-authorization for 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

3. Documentation member is currently stable on an oral corticosteroid regimen for at least 3 months and is expected to remain on stable corticosteroid regimen, unless contraindicated or member has experienced clinically significant adverse effects
   AND
4. Prescriber attests baseline platelet counts and triglycerides will be obtained prior to starting Duvyzat and monitoring will be done as clinically indicated per FDA label
   AND
5. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Duvyzat (givinostat) include: Avoid use in patients who are at an increased risk for ventricular arrhythmias, avoid concomitant use with other drugs that prolong the QTc interval, do not initiate in patients with a platelet count less than 150 x 10^9/L.]

CONTINUATION OF THERAPY:

A. DUCHENNE MUSCULAR DYSTROPHY (DMD):
1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
   AND
2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity (i.e., ventricular arrhythmias, elevated triglycerides, or diarrhea unresponsive to dose modification)
   AND
3. Documentation of positive clinical response as demonstrated by low disease activity and/or improvements in the condition's signs and symptoms [DOCUMENTATION REQUIRED]
   AND
4. Prescriber attests platelet counts and triglycerides are monitored as clinically indicated per FDA label

DURATION OF APPROVAL:

Initial authorization: 12 months, Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:

Prescribed by, or in consultation with, a board-certified neurologist, neuromuscular disorder specialist,

orthopedic specialist, physical medicine and rehabilitation specialist, neurodevelopmental disability specialist, or physician experienced in the treatment of Duchenne muscular dystrophy (DMD). [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:
6 years of age and older

QUANTITY:
Oral suspension twice daily based on actual body weight

Weight	Dosage	Oral Suspension Volume
10 kg to less than 20 kg	22.2 mg twice daily	2.5 mL twice daily
20 kg to less than 40 kg	31 mg twice daily	3.5 mL twice daily
40 kg to less than 60 kg	44.3 mg twice daily	5 mL twice daily
60 kg or more	53.2 mg twice daily	6 mL twice daily

PLACE OF ADMINISTRATION:
The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Muscular Dystrophy - Histone Deacetylase Inhibitors

FDA-APPROVED USES:
Indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients 6 years of age and older

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 rapidly.

- 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)

- 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 Duchenne muscular dystrophy (DMD) 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

Duvyzat (givinostat)

Duvyzat (givinostat) is a histone deacetylase (HDAC) inhibitor that modifies the deregulated activity of HDACs in the dystrophic muscle that result from the lack of dystrophin associated with DMD. The inhibition

of HDAC may activate repair mechanisms that can prevent muscle degeneration and reduce inflammation. Duvyzat's mechanism of action has the potential to inhibit the pathological changes associated with HDAC overactivity and address the cascade of events leading to muscle damage, thereby reducing the disease pathology, and slowing down muscle deterioration.

Clinical Evidence

The effectiveness of DUVYZAT for the treatment of Duchenne muscular dystrophy (DMD) was evaluated in a randomized, double-blind, placebo-controlled 18-month study (Study 1; NCT02851797). A total of 179 patients were randomized 2:1 to receive either DUVYZAT (n = 118) or placebo (n = 61). A weight-based dose regimen was applied [see Dosage and Administration (2.2)]. The study included male patients 6 years of age and older with a confirmed diagnosis of DMD who were ambulatory and on a stable dosage of corticosteroids.

At baseline, patients had a mean age of 9.8 years, 90% were White, 3% were Asian, 3% were Black. The primary endpoint was the change from baseline to Month 18 in 4-stair climb (4SC) time for DUVYZAT compared to placebo. The 4SC is a measure of muscle function that tests the time it takes to climb 4 stairs. A secondary efficacy endpoint was change from baseline to Month 18 in physical function as assessed by the North Star Ambulatory Assessment (NSAA).

The primary analysis population was based on a prespecified range of baseline muscle fat fraction as determined by MR spectroscopy. Patients treated with DUVYZAT showed statistically significant less decline in the 4-stair climb compared to placebo.

Patients treated with givinostat experienced less worsening on the NSAA compared to placebo, which was nominally significant but not statistically significant based on the prespecified multiplicity adjustment.

Of note, the study protocol was amended to reduce the starting dose by almost 50% due to tolerability. A post-hoc analysis of covariance (ANCOVA) suggested that the treatment effect was not affected by the change in treatment regimen (P = 0.63)

Table 4. Change from Baseline to Month 18 on 4SC Compared to Placebo*

	Mean Baseline 4SC (seconds)	Mean Change from Baseline	Treatment Difference from Placebo (95% CI)	p-value
DUVYZAT (n = 81)	3.39	1.25	-1.78 (-3.46, -0.11)	0.037
Placebo (n = 39)	3.48	3.03		

*Givinostat or placebo were administered in addition to a stable dose of corticosteroids throughout the study

Safety

The most common adverse reactions reported with Duvyzat were diarrhea, abdominal pain, thrombocytopenia, nausea/vomiting, hypertriglyceridemia, and pyrexia. Treatment-related adverse events and adverse events leading to dose reduction were more common with Duvyzat than with placebo and included diarrhea, abdominal pain, vomiting/nausea, thrombocytopenia, and hypertriglyceridemia. Of the 118 receiving givinostat, 28% (33) had a dose reduction due to a decreased platelet count, (42% (23) of 55 on Regimen 1 and 16% (10) of 63 on Regimen 2). Overall, 2% of the patients discontinued the study because of an adverse reaction

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Duvyzat (givinostat) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Duvyzat (givinostat) include: Avoid use in patients who are at an increased risk for ventricular arrhythmias, avoid concomitant use with other drugs that prolong the QTc interval, do not initiate in patients with a platelet count less than 150 x 10^9/L.

OTHER SPECIAL CONSIDERATIONS:
None

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
NA	

AVAILABLE DOSAGE FORMS:
Duvyzat SUSP 8.86MG/ML
NDC 11797-0110-01: One bottle containing 140 mL of oral suspension; each mL contains 8.86 mg of givinostat
NDC 11797-0110-02: Carton, includes one bottle containing 140 mL oral suspension, one 5 mL graduated oral syringe

REFERENCES

1. Duvyzat (givinostat) oral suspension [prescribing information]. Concord, MA: ITF Therapeutics, LLC; March 2024.
2. Mercuri E, et al. Safety and efficacy of givinostat in boys with Duchenne muscular dystrophy (EPIDYS): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol. 2024;23(4):393-403. doi:10.1016/S1474-4422(24)00036-X
3. U.S. Food and Drug Administration. FDA approves nonsteroidal treatment for Duchenne muscular dystrophy. News release. March 21, 2024. https://www.fda.gov/news-events/press-announcements/fda-approves-nonsteroidaltreatment-duchenne-muscular-dystrophy

SUMMARY OF REVIEW/REVISIONS	DATE
NEW CRITERIA CREATION	Q3 2024