09-J4000-86

Original Effective Date: 10/01/24

Reviewed: 08/14/24

Revised: 00/00/00

Subject: Givinostat HCl (Duvyzat)

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DESCRIPTION:

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. This X-linked recessive disorder is caused by mutations (mainly deletions) in the dystrophin gene that lead to an absence or defect in the dystrophin protein.

Dystrophin is thought to maintain the structural integrity of the muscle cell membrane by connecting the cytoskeleton to the underlying extracellular matrix, and acting as a scaffold for several molecules that also contribute to normal muscle physiology. Absence of dystrophin leads to mitochondrial dysfunction and damage, with inflammatory processes also appearing to contribute to muscle pathology. Muscle fibers ultimately undergo necrosis with replacement by adipose and connective tissue. Principal disease manifestations include progressive degeneration of skeletal and cardiac muscle, leading to loss of physical function in childhood and adolescence with premature death from respiratory and/or cardiac failure in the second to fourth decade.

As males have only one X chromosome, and thus 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. DMD has an estimated incidence of 1 in 3,500 male births. Available data suggests around 83% of DMD patients have genotypes amenable to exon skipping, and that 13% of DMD patients have genotypes that are amenable to exon 51 skipping.

Treatment options for DMD predominantly focus on management of symptoms and secondary complications. Glucocorticoids are the only pharmacological treatments that have been shown to improve skeletal muscle strength and function in reproducible randomized controlled trials; they also reduce the risk of scoliosis, stabilize pulmonary function, and may also improve cardiac function. Current

guidelines recommend initiation of glucocorticoids (such as prednisolone) once patients reach a plateau of motor skill development, generally at age 4-6 years, but prior to onset of motor decline. Gene-based therapies including exon skipping therapies (Exondys 51, Vyondys 53, Viltepso, Amondys 45) and Elevidys are approved for the treatment of DMD. These therapies increase dystrophin expression, but clinical benefit has not been established in a phase 3 study.

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.

Givinostat (Duvyzat), a novel histone deacetylase (HDAC) inhibitor, was approved by the U.S. Food and Drug Administration (FDA) in 2024 for treatment of DMD in patients 6 years of age and older. The exact mechanism by which givinostat works in patients with DMD is unknown – HDACs are enzymes that regulate the deacetylation of numerous histone and non-histone proteins, affecting a wide range of cellular processes. Expression and activity of HDAC are higher in dystrophic skeletal muscles, suggesting a role for these enzymes in the progression of the disease. Histone deacetylase inhibitors may inhibit fibro-adipogenic degeneration while promoting muscle regeneration and enhancing the process of skeletal myogenesis..

The approval of givinostat was based on a randomized, double-blind, placebo controlled, phase 3 clinical trial (EPIDYS, NCT02851797). Eligible participants were ambulant, male, and at least 6 years of age, had a genetically confirmed diagnosis of DMD, completed two four-stair climb assessments with a mean of 8 s or less (≤1 s variance), had a time-to-rise of at least 3 s but less than 10 s, and had received systemic corticosteroids for at least 6 months.

Participants were randomly assigned 2:1 to receive either oral givinostat or matching placebo twice a day for 72 weeks, stratified by concomitant steroid use. The dose was flexible, based on weight, and was reduced if not tolerated. Boys were divided into two groups on the basis of their baseline vastus lateralis fat fraction (VLFF; measured by magnetic resonance spectroscopy): group A comprised boys with a VLFF of more than 5% but no more than 30%, whereas group B comprised boys with a VLFF of 5% or less, or more than 30%. The primary endpoint compared the effects of givinostat and placebo on the change in results of the four-stair climb assessment between baseline and 72 weeks, in the intention-to-treat, group A population.

Of the 179 boys enrolled, 120 (67%) were in group A (81 givinostat and 39 placebo); of these, 114 (95%) completed the study. Treatment with givinostat resulted in a smaller decline in four-stair climb results at 72 weeks compared with placebo (geometric least squares mean ratios, 1.27 vs 1.48; treatment effect, 0.86 [95% CI, 0.75 to 0.99]), with changes from baseline of 1.25 seconds compared with 3.03 seconds. The differences from baseline in the North Star Ambulatory Assessment (NSAA) total score, cumulative loss of function, time-to-rise, and 6-minute walk test were numerically but not significantly different between givinostat and placebo at 72 weeks. The most common adverse events in the givinostat group were diarrhea (43 [36%] of 118 boys vs 11 [18%] of 61 receiving placebo) and vomiting (34 [29%] vs 8 [13%]); no treatment-related deaths occurred.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility **does not meet the definition of medical necessity**.

Initiation of givinostat (Duvyzat) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member is diagnosed with Duchenne Muscular Dystrophy (DMD)
2. Member's DMD diagnosis is confirmed by genetic testing – laboratory results must be provided
3. Member has tried and had an inadequate response to treatment with systemic corticosteroids for at least 6 months – documentation from the medical record must be provided
4. Member provides a baseline score from two assessments of a four stairs climb (4SC) test with results within 1 second of each other AND the mean score of less than or equal to 8 seconds – documentation from the medical record must be provided
5. Member is ambulatory and not wheelchair dependent – documentation from the medical record must be submitted
6. Member is 6 years of age or older
7. Dose does not exceed the following based on actual body weight:
    a. 10 kg to less than 20 kg: 22.2 mg twice daily (2.5 mL twice daily)
    b. 20 kg to less than 40 kg: 31 mg twice daily (3.5 mL twice daily)
    c. 40 kg to less than 60 kg: 44.3 mg twice daily (5 mL twice daily)
    d. 60 kg or more: 53.2 mg twice daily (6 mL twice daily)

Approval duration: 6 months

Continuation of givinostat (Duvyzat) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Authorization/reauthorization has been previously approved by Florida Blue in the past two years for treatment of DMD, OR the member has previously met all indication-specific initiation criteria
2. Member's DMD diagnosis is confirmed by genetic testing – laboratory results must be provided
3. Member is ambulatory and not wheelchair dependent – documentation from the medical record must be submitted
4. Dose does not exceed the following based on actual body weight:
    a. 10 kg to less than 20 kg: 22.2 mg twice daily (2.5 mL twice daily)

b. 20 kg to less than 40 kg: 31 mg twice daily (3.5 mL twice daily)

c. 40 kg to less than 60 kg: 44.3 mg twice daily (5 mL twice daily)

d. 60 kg or more: 53.2 mg twice daily (6 mL twice daily)

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- The recommended twice daily dose is based on body weight:
  - 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)

Dose Adjustments

- See FDA approved labeling for dose adjustments due to adverse events

Drug Availability

- Oral Suspension: 8.86 mg/mL

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- Hematological Changes: DUVYZAT can cause dose-related thrombocytopenia and other signs of myelosuppression, including anemia and neutropenia. Monitor platelets; dosage adjustment or discontinuation may be needed.
- Increased Triglycerides: An increase in triglycerides can occur; dosage modification may be needed. Discontinuation may be needed.
- Gastrointestinal Disturbances: Adjust dosage if moderate or severe diarrhea occurs. Antiemetics or antidiarrheal medications may be considered during treatment with DUVYZAT. Discontinue DUVYZAT if the symptoms persist.

- QTc Prolongation: Avoid use of DUVYZAT in patients who are at an increased risk for ventricular arrhythmias.

BILLING/CODING INFORMATION:

HCPCS Coding

J3490	Unclassified drugs

ICD-10 Diagnosis Codes That Support Medical Necessity

G71.01	Duchenne or Becker muscular dystrophy

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

6 minute walk test: assesses distance walked over 6 minutes as a sub-maximal test of aerobic capacity/endurance

9 Hole Peg Test: a brief, standardized quantitative test of upper extremity function

Maximum Voluntary Isometric Contraction Test: assesses muscle strength

North Star Ambulatory Assessment: a functional scale designed for ambulant boys affected by DMD

RELATED GUIDELINES:

Eteplirsen (Exondys 51), 09-J2000-69

OTHER:

None

REFERENCES:

1. Bushby K, Finkel R, Birnkrant DJ, et al; Duchenne Muscular Dystrophy Care Considerations Working Group. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol. 2010 Jan;9(1):77-93.
2. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc.; 2024 [cited 07/30/24]. Available from: http://www.clinicalpharmacology.com/.
3. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine; 2000 Feb 29 - [cited 07/30/24]. Available from: http://clinicaltrials.gov/.
4. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 07/30/24].
5. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2024 [cited 07/30/24]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 08/14/24.

GUIDELINE UPDATE INFORMATION:

10/01/24	New Medical Coverage Guideline.