TEMPLATE
Letter of Medical Necessity
For Medical Procedures Associated with the Administration of DUVYZAT (Givinostat)

Date:

[Insert Name of Medical Director] RE: Patient Name [ ]

[Insurance Company] Policy Number [ ]

[Address] Claim Number [ ]

[City, State, Zip]

Dear [Insurance Company]:

I am writing this letter of medical necessity to provide information related to the treatment of [insert patient name] with DUVYZAT (givinostat), a histone deacetylase inhibitor for the treatment of Duchenne muscular dystrophy in individuals 6 years of age and older. The FDA approval of DUVYZAT was based on results of a phase 3 trial.

I would like to provide the following information about the potential benefit of DUVYZAT in Duchenne patients:

1. Duchenne pathophysiology

Duchenne muscular dystrophy (DMD) is an X-linked genetic disorder characterized by the progressive loss of muscle, primarily in boys. DMD is the result of variants in the dystrophin (*DMD*) gene. It affects one out of 5000 live male births in the US.[3,4] The average age at diagnosis is approximately five years[5] but delays in motor milestones (such as sitting, standing independently, climbing, and walking) occur much earlier.[6]

Dystrophin is located beneath the sarcolemma, and functions to connect the subsarcolemmal cytoskeleton to the sarcolemma. A loss of dystrophin in muscle results in inflammation, muscle degeneration, and replacement of muscle with fibroadipose (fat and fibrotic) tissue. The primary symptoms of Duchenne muscular dystrophy are caused by a lack of dystrophin in the muscle. Children with Duchenne lose the ability to walk independently and most become reliant on wheelchairs for mobility by the age of 13.[7] Most individuals with Duchenne experience serious respiratory, orthopedic, and cardiac complications. By the age of 18, the majority of patients require ventilation support at night.[8] The average life expectancy is approximately 30 years of age, with respiratory complications and cardiomyopathy being common causes of death.[8] Standard medical management of Duchenne requires attention to the use of corticosteroids as well as respiratory, cardiac, orthopedic, and rehabilitative interventions aimed at the sequela that progressively worsen throughout the lifespan of Duchenne.[8] Corticosteroids slow the

progression of muscle weakness and delay some of the complications of the disease, but they do not treat or correct the underlying causes of Duchenne.

2. Description of DUVYZAT[2]

DUVYZAT (givinostat) oral suspension contains givinostat hydrochloride monohydrate, a histone deacetylase inhibitor. Givinostat hydrochloride monohydrate is designated chemically as: [6-(diethylaminomethyl)naphthalen-2-yl]methyl[4(hydroxycarbamoyl) phenyl] carbamate hydrochloride monohydrate.[2]

3. Mechanism of action and clinical trial results of DUVYZAT [2]

DUVYZAT is a histone deacetylase inhibitor. The precise mechanism by which DUVYZAT exerts its effect in patients with DMD is unknown. [2]

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.

4. Dosing Schedule of DUVYZAT [2]

The recommended dosage of DUVYZAT is based on body weight and administered orally twice daily with food (see Table 1) [see Dosage and Administration (2.4)].

Table 1: Recommended Dosage in Patients 6 Years of Age and Older for the Treatment of DMD

Weight	Dosage	Oral Suspension Volume
10kg to less than 20kg	22.2 mg twice daily	2.5 ml twice daily
20kg to less than 40kg	31 mg twice daily	3.5 mil twice daily
40kg to less than 60kg	44.3 mg twice daily	5 ml twice daily

60kg or more	53.2 mg twice daily	6 ml twice daily

6. Rationale for Treatment

I believe DUVYZAT supplied to my patient is medically necessary to help preserve muscle, delaying loss of function.[1] Data generated from givinostat studies to date[9,10] support it to be functionally significant to patients and reasonably likely to predict clinical benefit.

7. Summary of Patient's History [You should also include]:

- Chart notes, including the patient's most recent weight
- Genetic tests
- Copy of the patient's insurance cards
- FDA Approval Letter
- Prescribing information
- Recent medical articles
- Letters from other specialists treating the patient such as cardiologists, pulmonologists and physical and occupational therapists
- Patient's psychological factors that are relevant to your chosen treatment
- Side effects associated with other steroids trialed
- Information to educate Medical Director or Pharmacy Director who is not familiar with the disease or treatment

8. Patient's prognosis

- Summary of your professional opinion of the patient's likely prognosis without treatment with DUVYZAT. If applicable, consider including rationale for maintaining additional therapies with dosing of DUVYZAT.

9. Concluding Remarks

Based on the clinical data available to date, it is my medical opinion that initiating treatment of **[patient name]** with DUVYZAT is medically appropriate and necessary and the procedures required for its administration should be a covered and reimbursed service. This letter outlines **[patient name's]** medical history, prognoses, and the rationale for treatment with DUVYZAT.

Please call my office at **[insert telephone number]** if I can provide you with any additional information. I look forward to receiving your timely response and approval of this claim.

Sincerely,

[Insert Doctor name and
Participating provider number]

References

[1]*U.S. Food and Drug Administration, NDA 217865 approval letter, March 21st 2024.* https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2024/217865Orig1s000ltr.pdf
[2]*DUVYZAT (givinostat) [package insert]. Silver Spring, MD: U.S. Food & Drug Administration.* https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/217865Orig1s000lbl.pdf *Published March, 2024.*

[3]*Mendell JR, Shilling C, Leslie ND, et al. Evidence Based Path to Newborn Screening for Duchenne Muscular Dystrophy. Ann Neurol 2012;71:304-313.*
[4]*Mah JK, Korngut L, Dykeman J, Day L, Pringsheim T, Jette N. A systematic review and meta-analysis on the epidemiology of Duchenne and Becker muscular dystrophy. 2014;24:482-491.*
[5]*Ciafaloni E, Fox DJ, Pandya S, Westfield CP, Puzhankara S, Romitti PA, et al. Delayed diagnosis in Duchenne muscular dystrophy: data from the muscular dystrophy surveillance, tracking, and research network (MD-STARnet). J Pediatr 2009;155:380-385.*
[6]*Bushby K, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management Lancet Neurol 2018*
[7]*Bello L, Gordish-Dressman H1, Morgenroth LP1, Henricson EK1, Duong T1, Hoffman EP1, Cnaan A1, McDonald CM2; CINRG Investigators. Prednisone/prednisolone and deflazacort regimens in the CINRG Duchenne Natural History Study. Neurology. 2015*
[8]*Birnkrant DJ, Bushby K, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management Lancet Neurol 2018*
[9]*Mercuri E, Vilchez JJ, Boespflug-Tanguy O, Zaidman CM, Mah JK, Goemans N, 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
[10]*Vandenborne K, Willcocks R, Walter G, Forbes S, Cazzaniga S, Bettica P, Mercuri E, McDonald C P129 Givinostat in DMD: results of the Epidys study with particular attention to MR measures of muscle fat fraction Neuromuscular Disorders 2023*