PDL DRUG REVIEW

Proprietary Name: Duvyzat®
Common Name: givinostat suspension
PDL Category: Muscular Dystrophy Agents

Comparable Products	Preferred Drug List Status
Emflaza	Preferred with Conditions

Pharmacology/Usage: Givinostat, the active ingredient of Duvyzat®, is a histone deacetylase inhibitor. The exact mechanism of use for its approved indication is not known.

Indication: For the treatment of Duchenne muscular dystrophy (DMD) in patients 6 years of age and older.

There is no pregnancy category for this medication; however, the risk summary indicates that Duvyzat® is indicated for the treatment of DMD, which is a disease of mainly young male patients. Thus, there are no adequate data available to assess the use in pregnant women. The safety and efficacy of use in the pediatric population below the age of 6 years have not been established.

Dosage Form: Oral Suspension: 8.86mg/ml, as a peach-cream flavored suspension.

Recommended Dosage: Obtain and assess baseline platelet counts and triglycerides prior to the start of Duvyzat®. Do not start Duvyzat® in patients with a platelet count less than 150 X 10^9/L. Monitor platelet counts and triglycerides as recommended during treatment to determine if dosage modifications are needed.

In addition, in patients with underlying cardiac disease or taking concomitant medications that cause QT prolongation, obtain ECGs when starting treatment with Duvyzat®, during concomitant use, and as clinically indicated.

Before use, shake Duvyzat® suspension for at least 30 seconds. Using a graduated oral syringe, measure the appropriate volume of suspension corresponding to the prescribed dose. Administer orally with the provided graduated oral syringe.

The recommended dosage of Duvyzat® is based on body weight and administered orally twice daily with food. Refer to the table below for the recommended dosage in patients 6 years of age and older, which was adapted from the prescribing information.

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

Weight	Dosage	Oral Suspension Volume
60kg or more	53.2mg BID	6ml BID

If a dose is missed, patients should not take double or extra doses.

Duvyzat® may cause adverse reactions, which may necessitate a dosage modification if the following occur:

- Platelet count <150 X 10^9/L verified in two assessments one week apart, or
- Moderate or severe diarrhea, or
- Fasting triglycerides >300mg/dL verified by two assessments one week apart.

Based on the severity of these adverse reactions, treatment interruption prior to dosage modification should be considered. Refer to the prescribing information for additional information on dosage modifications for adverse reactions.

Withhold Duvyzat® if the QTc interval is >500ms or the change from baseline is >60ms.

A dedicated clinical study was not conducted to assess the pharmacokinetics of Duvyzat® in subjects with hepatic impairment, and no recommendation for dosage adjustment can be made for patients with hepatic impairment. As Duvyzat® is eliminated mainly thought hepatic metabolism, hepatic impairment is expected to increase the exposure of givinostat.

Drug Interactions: Givinostat is a weak intestinal CYP3A4 inhibitor. Closely monitor when Duvyzat® is used in combination with orally administered CYP3A4 sensitive substrates for which a small change in substrate plasma concentration may lead to serious toxicities.

Givinostat is a weak inhibitor of the renal uptake transporter OCT2. Closely monitor when Duvyzat® is used in combination with drugs known as a sensitive substrate of the OCT2 transporter for which a small change in substrate plasma concentration may lead to serious toxicities.

Duvyzat® causes QTc interval prolongation. Concomitant use of Duvyzat® with other products that prolong the QTc interval may result in a greater increase in the QTc interval and adverse reactions associated with QTc interval prolongation, including Torsade de pointes, other serious arrhythmias, and sudden death. Avoid concomitant use of Duvyzat® with other product(s) with a known potential to prolong the QTc interval. If concomitant use cannot be avoided, obtain ECGs when starting, during concomitant use, and as clinically indicated. Withhold Duvyzat® if the QTc interval is >500ms or the change from baseline is >60ms.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Duvyzat®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included diarrhea (17%), abdominal pain (9%), thrombocytopenia (33%), nausea/vomiting (14%), hypertriglyceridemia (16%), pyrexia (5%), myalgia (6%), rash (7%), arthralgia (6%), fatigue (8%), constipation (5%), and decreased appetite (7%). Adverse reactions of hypothyroidism and/or thyroid stimulating hormone (TSH) increased occurred in 5% of patients treated with Duvyzat® compared to 2% of patients who received placebo.

Duvyzat® can cause dose-related thrombocytopenia and other signs of myelosuppression, including decreased hemoglobin and neutropenia. In study 1, thrombocytopenia occurred in 33% of patients treated with Duvyzat® compared with no patients treated with placebo. The maximum decrease in platelets occurred within the first 2 months of therapy and remained low throughout the course of therapy. Patients with baseline platelet counts below the lower limit of normal were excluded from the study. Decreased hemoglobin and decreased neutrophils were also observed in patients treated with Duvyzat® compared to placebo. Monitor blood counts every 2 weeks for the

first 2 months of treatment, at month 3, and then every 3 months thereafter. Modify the dosage of Duvyzat® for confirmed thrombocytopenia. Treatment should be permanently discontinued if the abnormalities worsen despite dose modification.

Duvyzat® can cause elevations in triglycerides. Monitor triglycerides at 1 month, 3 months, 6 months, and then every 6 months thereafter. Modify the dosage if fasting triglycerides are verified >300mg/dL. Treatment with Duvyzat® should be discontinued if triglycerides remain elevated despite adequate dietary intervention and dosage adjustment.

Gastrointestinal disturbances, including diarrhea, nausea/vomiting, and abdominal pain, were common adverse reactions in Duvyzat® clinical trials. Diarrhea usually occurred within the first few weeks of the start of treatment. Vomiting and nausea, sometimes severe and usually occurring within the first 2 months of treatment, occurred in 32% of patients treated with Duvyzat® compared to 18% of patients on placebo. One case of abdominal pain was serious. Antiemetics or antidiarrheal medications may be considered during treatment with Duvyzat®. Fluid and electrolytes should be replaced as needed to prevent dehydration. Modify the Duvyzat® dosage in patients with moderate or severe diarrhea, and treatment should be discontinued if significant symptoms persist.

Duvyzat® can cause prolongation of QTc interval. Avoid use of Duvyzat® in patients who are at an increased risk for ventricular arrhythmias, such as those with congenital long QT syndrome, coronary artery disease, electrolyte disturbance, and concomitant use of other medicinal products known to cause QT prolongation. Obtain ECGs prior to starting treatment with Duvyzat® in patients with underlying cardiac disease or in patients who are taking concomitant medications that cause QT prolongation.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Italfarmaco SA; Distributed by ITF Therapeutics, LLC

Analysis: The efficacy of Duvyzat® for the treatment of DMD was assessed in a randomized, double-blind, placebo-controlled study of 18 months duration that included patients (N=179) randomized to receive either Duvyzat® (N=118) or placebo (N=61). 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, while 90% were white.

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® demonstrated 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. The table below, which was adapted from the prescribing information, presents the change from baseline to month 18 on 4SC.

	Mean Baseline 4SC (Seconds)	Mean change from baseline	Treatment difference from placebo	p-value
Duvyzat® (N=81)	3.39	1.25	-1.78	0.037
Placebo (N=39)	3.48	3.03		

Place in Therapy: Duvyzat® is a histone deacetylase inhibitor indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients 6 years of age and older. Obtain and assess baseline platelet counts and triglycerides

prior to the start of treatment, and do not start treatment in patients with a platelet count less than 150 X 10^9/L. Monitor platelet counts and triglycerides as recommended during treatment to assess if dosage modifications are needed. In addition, in patients with underlying cardiac disease or taking concomitant medications that cause QT prolongation, obtain ECGs when starting treatment with Duvyzat®, during concomitant use, and as clinically indicated. The efficacy of Duvyzat® was assessed in a randomized, double-blind study that 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. The primary endpoint was the change from baseline to month 18 in 4-stair climb (4SC) time for Duvyzat® as compared to placebo. Results suggested that patients treated with Duvyzat® demonstrated statistically significant less decline in the 4SC compared to placebo. Duvyzat® is the first FDA approved oral non-steroidal treatment for DMD patients 6 years of age and older irrespective of their genetic variant or ability to walk. Note that the phase 3 trial did not include patients who were not able to walk on their own.

Summary

There is no evidence at this time to support that Duvyzat® is safer or more effective than the other currently preferred, more cost-effective medications. It is therefore recommended that Duvyzat® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred with Conditions (DUR to develop PA criteria)**

References

[1] Duvyzat [package insert]. Concord, MA: ITF Therapeutics, LLC; 2024.

Prepared By: Iowa Medicaid Date: 02/17/2025