HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DUVYZAT safely and effectively. See full prescribing information for DUVYZAT.

DUVYZAT (givinostat) oral suspension
Initial U.S. Approval: 2024

----------INDICATIONS AND USAGE----------
DUVYZAT is a histone deacetylase inhibitor indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients 6 years of age and older. (1)

----------DOSAGE AND ADMINISTRATION----------
- Obtain and evaluate baseline platelet counts and triglycerides prior to initiation of DUVYZAT. Do not initiate DUVYZAT in patients with a platelet count less than 150 x 10^9/L. (2.1, 5.1, 5.2)
- The dosage of DUVYZAT is based on patient's body weight. (2.2)
- Administer orally twice daily with food. (2.2)
- Dosage modifications may be needed for decreased platelet counts, diarrhea, increased triglycerides, or QTc prolongation. (2.3, 5.1, 5.2, 5.3, 5.4)

----------DOSAGE FORMS AND STRENGTHS----------
Oral suspension: 8.86 mg/mL givinostat. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
- 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. (2.3, 5.1)
- Increased Triglycerides: An increase in triglycerides can occur; dosage modification may be needed. Discontinuation may be needed. (2.3, 5.2)
- 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. (2.3, 5.3)
- QTc Prolongation: Avoid use of DUVYZAT in patients who are at an increased risk for ventricular arrhythmias. (2.1, 5.4, 7.2)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥10% in DUVYZAT-treated patients) are diarrhea, abdominal pain, thrombocytopenia, nausea/vomiting, hypertriglyceridemia, and pyrexia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ITF Therapeutics, LLC. at 1-833-582-4312 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Closely monitor when DUVYZAT is used in combination with an oral CYP3A4 sensitive substrate or a sensitive substrate of the OCT2 transporter, for which a small change in substrate plasma concentration may lead to serious toxicities. (7.1)
- Avoid concomitant use with other drugs that prolong the QTc interval; monitor ECG if concomitant use cannot be avoided. (7.2)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Hepatic Impairment: Exposure to givinostat is expected to be increased. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2024

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

DUVYZAT is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients 6 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Evaluation and Testing Before Initiation of DUVYZAT

Obtain and evaluate baseline platelet counts and triglycerides prior to initiation of DUVYZAT *[see Warnings and Precautions (5.1, 5.2)]*. Do not initiate 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 *[see Dosage and Administration (2.3)].*

In addition, in patients with underlying cardiac disease or taking concomitant medications that cause QT prolongation, obtain ECGs when initiating treatment with DUVYZAT, during concomitant use, and as clinically indicated *[see Dosage and Administration (2.3), Warnings and Precautions (5.4), and Drug Interactions (7.2)].*

2.2 Recommended Dosage

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
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

± Based on actual body weight

2.3 Dosage Modifications for Adverse Reactions

Decrease in Platelets, Diarrhea, Increase in Triglycerides

DUVYZAT may cause adverse reactions *[see Warnings and Precautions (5.1, 5.2, 5.3)],* which may necessitate a dosage modification (see Table 2*)* 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 >300 mg/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.

Table 2: Dosage Modifications for Adverse Reactions in Patients 6 Years of Age and Older for the Treatment of DMD

	First Dosage Modification*		**Second Dosage Modification****	
Weight±	**Dosage**	**Oral Suspension Volume**	**Dosage**	**Oral Suspension Volume**
10 kg to less than 20 kg	17.7 mg twice daily	2 mL twice daily	13.3 mg twice daily	1.5 mL twice daily
20 kg to less than 40 kg	22.2 mg twice daily	2.5 mL twice daily	17.7 mg twice daily	2 mL twice daily
40 kg to less than 60 kg	31 mg twice daily	3.5 mL twice daily	26.6 mg twice daily	3 mL twice daily
60 kg or more	39.9 mg twice daily	4.5 mL twice daily	35.4 mg twice daily	4 mL twice daily

± Based on actual body weight
* If the adverse reaction(s) persist after the first dosage modification, proceed to the second dosage modification.
** If the adverse reaction(s) persist after the second dosage modification, DUVYZAT should be discontinued.

QTc Interval Prolongation

Withhold DUVYZAT if the QTc interval is > 500 ms or the change from baseline is > 60 ms *[see Warnings and Precautions (5.4) and Drug Interactions (7.2)].*

2.4 Preparation and Administration Instructions

See the Instructions for Use for further details.

- Before use, shake the DUVYZAT suspension for at least 30 seconds by inverting the bottle by 180°.

- Visually verify the homogeneity of the suspension.
- Using a graduated oral syringe, measure the appropriate volume of suspension corresponding to the prescribed dose of DUVYZAT.
- Administer orally with the provided graduated oral syringe.

2.5 Missed Dose

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

3 DOSAGE FORMS AND STRENGTHS

Oral suspension: 8.86 mg/mL givinostat as a white to off-white or faintly pink, peach-cream flavored suspension.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hematological Changes

DUVYZAT can cause dose-related thrombocytopenia and other signs of myelosuppression, including decreased hemoglobin and neutropenia.

In Study 1 *[see Clinical Studies (14)],* thrombocytopenia occurred in 33% of patients treated with DUVYZAT compared to no patients on placebo. The maximum decrease in platelets occurred within the first 2 months of therapy and remained low throughout the course of therapy. In a few patients, thrombocytopenia was associated with bleeding events including epistaxis, hematoma or contusions. Low platelet counts resulted in DUVYZAT dose reduction in 28% of patients. 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 *[see Dosage and Administration (2.3)]*. Treatment should be permanently discontinued if the abnormalities worsen despite dose modification. If a patient develops signs or symptoms of thrombocytopenia, obtain a platelet count as soon as possible, and hold dosing until platelet count is confirmed.

5.2 Increased Triglycerides

DUVYZAT can cause elevations in triglycerides. In Study 1 *[see Clinical Studies (14)]*, hypertriglyceridemia occurred in 23% of patients treated with DUVYZAT (one of whom had familial hypertriglyceridemia) compared to 7% of patients on placebo. High triglycerides (i.e., levels greater than 300 mg/dL) resulted in discontinuation and led to dosage modification in 2% and 8%, respectively, of patients treated with DUVYZAT.

Monitor triglycerides at 1 month, 3 months, 6 months, and then every 6 months thereafter. Modify the dosage if fasting triglycerides are verified > 300 mg/dL *[see Dosage and Administration (2.3)].* Treatment with DUVYZAT should be discontinued if triglycerides remain elevated despite adequate dietary intervention and dosage adjustment.

5.3 Gastrointestinal Disturbances

Gastrointestinal disturbances, including diarrhea, nausea/vomiting, and abdominal pain were common adverse reactions in DUVYZAT clinical trials in DMD. In Study 1, diarrhea was reported in 37% of patients treated with DUVYZAT (with 1 severe case reported) compared to 20% of patients on placebo. Diarrhea usually occurred within the first few weeks of initiation of treatment with DUVYZAT.

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. Abdominal pain occurred in 34% of patients treated with DUVYZAT compared to 25% 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 *[see Warnings and Precautions (5.4)]*. Modify the dosage of DUVYZAT in patients with moderate or severe diarrhea, and treatment should be discontinued if significant symptoms persist *[see Dosage and Administration (2.3)].*

5.4 QTc Prolongation

DUVYZAT can cause prolongation of QTc interval *[see Clinical Pharmacology (12.2)].* Avoid use of DUVYZAT in patients who are at an increased risk for ventricular arrhythmias (including torsades de pointes), such as those with congenital long QT syndrome, coronary artery disease, electrolyte disturbance *[see Warnings and Precautions (5.3)]*, concomitant use of other medicinal products known to cause QT prolongation *[see Drug Interactions (7.2)]*. Obtain ECGs prior to initiating treatment with DUVYZAT in patients with underlying cardiac disease or in patients who are taking concomitant medications that cause QT prolongation *[see Dosage and Administration (2.1)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described below and elsewhere in the labeling:

- Hematological Changes *[see Warnings and Precautions (5.1)]*
- Increased Triglycerides *[see Warnings and Precautions (5.2)]*
- Gastrointestinal Disturbances *[see Warnings and Precautions (5.3)]*
- QTc Prolongation *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In controlled and uncontrolled trials in patients with confirmed DMD, 222 male patients aged 6 years and older were treated with DUVYZAT, including 210 patients treated for ≥ 6 months, 187 patients for ≥ 12 months, and 105 patients for ≥ 24 months.
The safety profile of DUVYZAT is based on a double-blind, placebo-controlled, 18-month study in a total of 179 ambulant DMD patients aged 6 years or older on concomitant steroid treatment (Study 1) *[see Clinical Studies (14)]*. The dosage in Study 1 was weight-based *[see Dosage and Administration (2.2)]*. Patients were excluded from the study if they had the following abnormalities at the screening visit: platelet, white blood cell, or hemoglobin counts less than the lower limit of normal, triglycerides > 300 mg/dL (3.42 mmol/L) in fasting condition, or had a baseline-corrected QT interval, Fridericia's correction (QTcF) of > 450 msec (mean of 3 consecutive readings 5 minutes apart) or a history of additional risk factors for torsades de pointes (e.g., heart failure, hypokalemia, or family history of long QT syndrome). Overall, 2% of the patients discontinued the study because of adverse reactions.

Adverse reactions reported in >5% of DUVYZAT-treated patients at a frequency at least 5% greater than that of the placebo group are presented in Table 3 below.

Table 3. Adverse Reactions Reported in >5% of DUVYZAT-Treated Patients and at Least 5% Greater than Placebo in Study 1

Adverse Reaction	**DUVYZAT N=118 %**	**Placebo N=61 %**
Diarrhea	37	20
Abdominal pain	34	25
Thrombocytopenia[1]	33	0
Nausea/Vomiting	32	18
Hypertriglyceridemia	23	7
Pyrexia	13	8

Adverse Reaction	DUVYZAT N=118 %	Placebo N=61 %
Myalgia	9	3
Rash	9	2
Arthralgia	8	2
Fatigue	8	0
Constipation	7	2
Decreased appetite	7	0

[1] Thrombocytopenia includes platelet count decreased and thrombocytopenia

Less Common Adverse Reactions in Study 1

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.

7 DRUG INTERACTIONS

7.1 Effect of DUVYZAT on Other Drugs

CYP3A4 Sensitive Substrates

Givinostat is a weak intestinal CYP3A4 inhibitor *[see Clinical Pharmacology (12.3)].* 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.

OCT2 Sensitive Substrates

Givinostat is a weak inhibitor of the renal uptake transporter OCT2 *[see Clinical Pharmacology (12.3)]*. 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.

7.2 Effect of Other Drugs on DUVYZAT

Drugs that Prolong the QTc Interval

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 initiating, during concomitant use, and as clinically indicated *[see Warnings and Precautions (5.4)].* Withhold DUVYZAT if the QTc interval is > 500 ms or the change from baseline is > 60 ms *[see Dosage and Administration (2.1)]*.

DUVYZAT causes QTc interval prolongation *[see Clinical Pharmacology (12.2)]*. 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 arrythmias, and sudden death *[see Warnings and Precautions (5.4)].*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

DUVYZAT is indicated for the treatment of DMD, which is a disease of predominantly young male patients. Therefore, there are no adequate data available to assess the use of DUVYZAT in pregnant women. In animal studies, oral administration of givinostat during organogenesis resulted in decreased fetal body weight and increased structural variations; oral administration during pregnancy and lactation resulted in increased embryofetal and offspring mortality and neurobehavioral changes in the offspring. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data
Oral administration of givinostat (0, 40, 80, or 160 mg/kg/day) to pregnant rats throughout organogenesis resulted in reduced fetal body weight at the highest dose tested and increases in the incidence of skeletal and visceral variations at the mid and high doses. The no-effect dose (40 mg/kg/day) for adverse effects on embryofetal development was associated with maternal plasma exposures (AUC) lower than that in humans at the maximum recommended human dose (MRHD) of 53.2 mg twice daily.

Oral administration of givinostat (0, 40, 80, or 160 mg/kg/day) to pregnant rabbits throughout organogenesis resulted in maternal death at the highest dose tested, resulting in too few fetuses to evaluate. No adverse effects on embryofetal development were observed at the low and mid doses. Plasma exposures (AUC) at the higher no-effect dose (80 mg/kg) for adverse effects on embryofetal development were approximately 4 times that in humans at the MRHD.

Oral administration of givinostat (0, 40, 80, or 160 mg/kg/day) to rats throughout pregnancy and lactation resulted in increases in embryofetal mortality, stillbirths, and offspring mortality at the highest dose tested. When offspring were tested postweaning (postnatal day 49), adverse effects on behavior (decreased open field activity) were observed at all doses. A no-effect dose for adverse developmental effects was not identified; plasma exposures (AUC) at the lowest dose tested were lower than that in humans at the MRHD.

8.2 Lactation

Risk Summary

There are no human or animal data to assess the effect of DUVYZAT or its metabolites on milk production, the presence of givinostat in milk, or the effects on the breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DUVYZAT and any potential adverse effects on the breastfed infant from DUVYZAT or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

No human data are available on the effect of DUVYZAT on reproductive potential.

Animal studies indicate possible adverse effects on reproduction *[see Nonclinical Toxicology (13.1)].*

8.4 Pediatric Use

The safety and effectiveness of DUVYZAT in children aged 6 years and older have been established *[see Clinical Studies (14)]*. Safety and effectiveness in pediatric patients below the age of 6 years have not been established.

Juvenile Animal Data

In a study in juvenile male and female rats, givinostat was orally administered at doses of 0, 10, 20, or 40 mg/kg on postnatal days (PND) 7 to 27, doses of 0, 15, 30, or 60 mg/kg/day on PNDs 28 to 48, and doses of 0, 15, 45, or 90 mg/kg/day on PNDs 49 to 92. Adverse effects on behavior (increased locomotor activity and decreased auditory startle prepulse inhibition) were observed at the high dose at the end of the dosing period. Adverse effects on locomotor activity, but not prepulse inhibition, were observed at the end of the recovery period primarily at the mid and high doses. Persistent decreases in bone density were observed at all doses tested. A no-effect dose for adverse effects on postnatal development was not identified; the lowest dose tested was associated with plasma exposures (AUC) less than that in humans at the MRHD.

8.5 Geriatric Use

DMD is largely a disease of children and young adults; therefore, there is no experience with DUVYZAT in geriatric DMD patients.

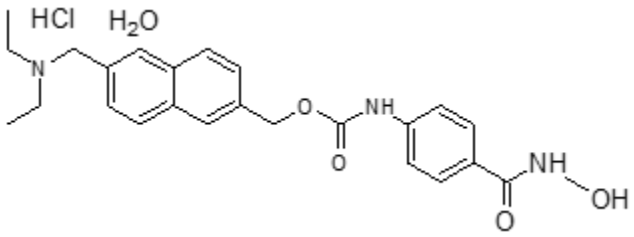
8.6 Hepatic Impairment

A dedicated clinical study was not conducted to evaluate the pharmacokinetics of DUVYZAT in subjects with hepatic impairment, and no recommendation for dosage

adjustment can be made for patients with hepatic impairment. Because DUVYZAT is eliminated mainly through hepatic metabolism, hepatic impairment is expected to increase the exposure of givinostat *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

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. The molecular formula is $C_{24}H_{27}N_3O_4$•HCl•H_2O and the molecular weight is 475.97 g/mol. Its structural formula is:



Givinostat hydrochloride monohydrate is a white to off-white, non-hygroscopic, crystalline powder that is very slightly to slightly soluble in aqueous media and slightly soluble in ethanol.

DUVYZAT contains givinostat 8.86 mg/mL (equivalent to givinostat hydrochloride monohydrate 10 mg/mL) and the following inactive ingredients: cream flavor, glycerin, non-crystallizing sorbitol solution, peach flavor, polysorbate 20, purified water, saccharin sodium, sodium benzoate, sodium hydroxide, tartaric acid, and tragacanth.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

Muscle Fat Fraction as Assessed by MR Spectroscopy

The percentage of fat fraction present in the vastus lateralis muscles (VLM) of the thigh was measured in Study 1 *[see Clinical Studies (14)]* using magnetic resonance spectroscopy. At 18 months, for the patients with VLM fat fraction baseline in the range of >5% to ≤30%, a mean increase (absolute difference from baseline levels) of VLM fat

fraction was 7.48% in the DUVYZAT-treated patients compared to a 10.89% increase in patients who received placebo.

Cardiac Electrophysiology

The largest mean increase in QTc interval of 13.6 ms (upper confidence interval of 17.1 ms) occurred 5 hours after administration of givinostat 265.8 mg to healthy subjects (approximately 5 times the 53.2 mg dose recommended for DMD patients weighing 60 kg or more) *[see Warnings and Precautions (5.4)]*.

12.3 Pharmacokinetics

Givinostat exhibits linear kinetics with the studied dose range. Systemic exposure to givinostat was dose-proportional across the therapeutic dose range. Steady-state concentrations are achieved within 5 to 7 days after twice daily dosing. An accumulation of less than 2-fold was observed for givinostat after twice daily administration.

Absorption

Absolute bioavailability was not determined. The time to maximum plasma concentrations is about 2 to 3 hours after oral administration.

Effect of Food
A high fat standard meal resulted in an increase in the exposure (about 40% increase in area under the plasma concentration-time curve [AUC] and about 23% increase in maximum plasma concentration [C_{max}]) and a delay in time to maximum concentration (T_{max}) from 2 to 3 hours *[see Dosage and Administration (2.2)].*

Distribution

Givinostat is approximately 96% bound to human plasma proteins and is slightly partitioned into red blood cells (blood to plasma ratio = 1.3).

Elimination

In plasma, apparent elimination half-life of givinostat is about 6 hours.

Metabolism
In vitro studies with human enzymatic preparations together with animal metabolism showed that givinostat is extensively metabolized forming several metabolites. CYP450 and UGTs are not involved in the main metabolic reactions. Four major metabolites, which are not active with respect to the efficacy of givinostat, have been characterized in humans and preclinical species.

Excretion

The elimination of givinostat is likely dependent on metabolism followed by renal and biliary excretion of the resulting metabolites as suggested by the mass balance study in the rat. Urinary excretion of givinostat in humans is minimal (<3% of the dose).

Specific Populations

The population PK analyses show that the PK of givinostat can be affected by body weight, while age has no effects on the pharmacokinetics of givinostat.

Patients with Hepatic Impairment
The pharmacokinetics and safety of givinostat have not been studied in patients with hepatic impairment. Givinostat is highly metabolized and therefore the impact of hepatic impairment on the exposure of givinostat cannot be excluded *[see Use in Specific Populations (8.6)].*

Patients with Renal Impairment
The pharmacokinetics and safety of givinostat have not been studied in patients with renal impairment. However, renal impairment is not expected to impact the exposure of givinostat because renal excretion is not a significant route of givinostat elimination.

Drug Interaction Studies

In Vitro
Givinostat is not a substrate of cytochrome P450 (CYP450) enzymes and uridine diphosphate glucuronosyltransferase (UGT). Therefore, coadministration of drugs that are inducers or inhibitors of major metabolizing enzymes will not significantly affect the systemic exposure of givinostat.

Givinostat and its metabolites ITF2374, ITF2375, ITF2440, and ITF2563 were investigated as inhibitors of the main CYP450 subfamilies, and the results indicated no inhibition is expected of CYP1A2, 2C9, 2C19, 2D6, 2B6, 2C8, and 3A4. Givinostat showed induction of CYP1A2, 2B6, and CYP3A4.

In vitro studies indicate that givinostat is a substrate of the intestinal transporters: P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Givinostat showed the potential to inhibit the intestinal transporter P-gp (MDR1) and BCRP based on in vitro results. However, these interactions are not expected to be clinically meaningful.

In Vivo
A weak inhibition of the renal uptake transporter OCT2 by givinostat was seen in clinical trials by creatinine (OCT2 substate) measurements *[see Drug Interactions (7.1)].*

A clinical drug interaction study was conducted in healthy volunteers to assess the effects of coadministration of givinostat with other drugs and results indicated that:

- givinostat has a weak inhibition of the intestinal CYP3A4 enzyme based on the exposure of a CYP3A4 substrate, midazolam, *[see Drug Interactions (7.1)]*

- givinostat does not likely inhibit P-gp transporters based on the exposure of dabigatran
- strong P-gp inhibitors have a weak effect on givinostat based on exposure of clarithromycin, which had an increase in C_{max} by about 40% without a significant change of AUC.

The effect of BCRP inhibitors on givinostat PK was not studied in a clinical study. However, the effect of BCRP inhibitors on givinostat PK is expected to be smaller than P-gp inhibitors based on the comparison of the two transporters mediated efflux ratios determined in the in vitro cell models.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Studies to assess the carcinogenic potential of givinostat have not been conducted.

Mutagenesis

Givinostat was positive in a bacterial reverse mutation (Ames) assay, and negative in an in vitro mammalian cell (mouse lymphoma) mutation assay, an in vitro chromosomal aberration assay in mammalian (human lymphocytes) cells, and an in vivo gene mutation assay (with Pig-a endpoints) in Big Blue transgenic rats.

Impairment of Fertility

Oral administration of givinostat (0, 40, 80, or 160 mg/kg) prior to and throughout mating in male and female rats and continuing to gestation day 7 in females, resulted in no adverse effects on fertility. However, there was an increase in corpora lutea at the mid and high doses and increased pre- and postimplantation loss at all doses. A no-effect dose for adverse effects on early embryonic development was not identified; plasma exposures (AUC) at the lowest dose tested were lower than that in humans at the maximum recommended human dose of 53.2 mg twice daily.

14 CLINICAL STUDIES

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 (see Table 4). 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.

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

DUVYZAT (givinostat) oral suspension is a white to off-white or faintly pink, peach-cream flavored suspension. It is supplied in an amber polyethylene terephthalate bottle closed with a high-density polyethylene child-resistant, screw cap with low-density polyethylene syringe adapter, containing 140 mL of oral suspension (NDC 11797-110-01). Each mL contains 8.86 mg of givinostat.

DUVYZAT is supplied in a carton, NDC 11797-110-02, containing:

- one bottle containing 140 mL oral suspension
- one 5 mL graduated oral syringe
- Prescribing Information and Instructions for Use

The Medication Guide is available at www.duvyzat.com/medication-guide.

16.2 Storage and Handling

Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Do not freeze. Store upright.

Discard any unused DUVYZAT remaining after 60 days of first opening of the bottle.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Administration Instructions

Instruct patients or caregivers to *[see Dosage and Administration (2.4)]:*

- Shake DUVYZAT oral suspension well before measuring out each dose.
- Administer using the provided graduated oral syringe to measure the appropriate volume of suspension corresponding to the prescribed dose for the patient.
- Take DUVYZAT with food.
- Discard any unused DUVYZAT oral suspension remaining after 60 days of first opening the bottle.

Hematological Changes

Inform patients and/or caregivers that DUVYZAT can cause hematological changes including a decrease in platelet counts (thrombocytopenia), anemia, and a decrease in neutrophils (neutropenia) *[see Warnings and Precautions (5.1)]*. Advise patients to notify their healthcare provider if they have any signs or symptoms of these adverse reactions (e.g., easy bruising, excessive bleeding from cuts, blood in the stool, fatigue). Instruct patients to adhere to the testing recommended to monitor for these adverse reactions. Inform patients that their dosage may need to be changed or their treatment may need to be stopped depending on the results of their test for platelet counts.

Increased Triglycerides

Inform patients and/or caregivers that DUVYZAT can cause an increase in triglycerides, *[see Warnings and Precautions (5.2)]*. Instruct patients to adhere to the testing recommended to monitor for this adverse reaction. Inform patients that their dosage may need to be changed or their treatment may need to be stopped depending on the results of their test for triglycerides.

Gastrointestinal Disturbances

Inform patients and/or caregivers that DUVYZAT can cause diarrhea and vomiting, which may require medication for treatment *[see Warnings and Precautions (5.3)]*. Advise patients to maintain hydration if diarrhea or vomiting occurs and contact their healthcare provider if the symptoms persist or become moderate to severe. Inform patients that their

dosage may need to be changed or their treatment may need to be stopped depending on the severity of diarrhea.

QTc Prolongation

Inform patients and/or caregivers that DUVYZAT can cause prolongation of the QTc interval *[see Warnings and Precautions (5.4)]*. Instruct patients to notify their healthcare provider if they have or develop any symptoms of significant QTc prolongation (e.g., dizziness, lightheadedness, syncope) or new cardiac issues and before taking any over-the-counter (e.g., diphenhydramine), herbal (e.g., echinacea), or prescription medications (e.g., antibiotics).

Manufactured by:
Italfarmaco S.A.
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Distributed by:
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