Duvyzat™ (givinostat)

Ryan, an actual DUVYZAT patient for 4+ years.

PROTECTION

AGAINST DMD PROGRESSION[1,2]

DMD, Duchenne muscular dystrophy.

Indication

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

Important Safety Information

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.

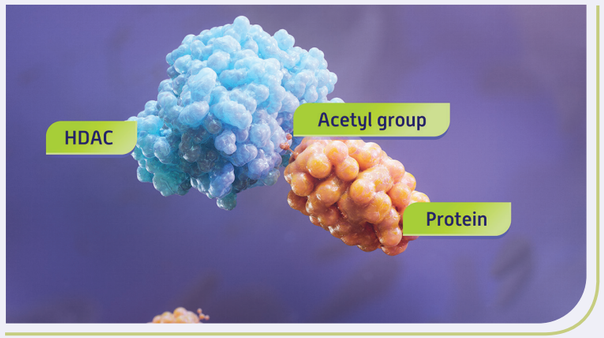
Please see full Important Safety Information on page 19.
Please see full Prescribing Information and Medication Guide in pocket.

While the exact mechanism is unknown,

DUVYZAT targets the key pathologic process of HDAC overactivity[1,3]

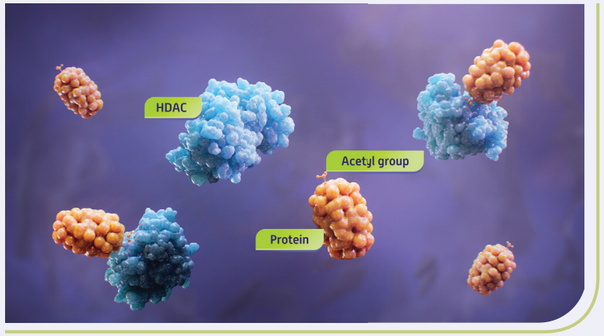
As a novel HDAC inhibitor, DUVYZAT is thought to work by targeting HDAC overactivity, leading to increased muscle fiber repair and regeneration, decreased inflammation, and reduced adipogenesis and fibrogenesis.[3,4]

Duvyzat™ (givinostat)



The role of HDAC in normal muscle repair[4]

HDACs play a key role in maintaining and repairing muscle tissue by modifying proteins that regulate muscle fiber repair pathways.



HDAC overactivity in DMD[2-4]

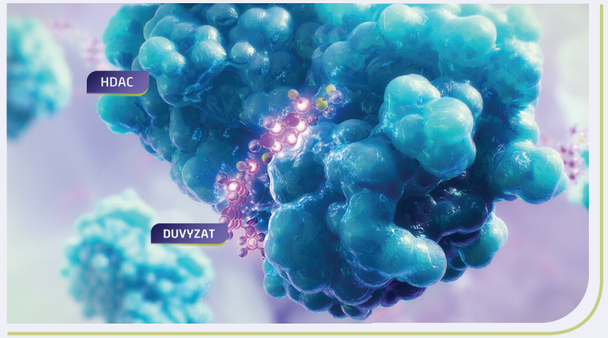
In DMD, HDAC is overactive.

Increased HDAC activity, in combination with the structural instability of dystrophin-deficient muscle cells, disrupts the process of normal muscle repair and accelerates the deterioration of tissue.

HDAC upregulation results in[2,4]:

- Activation of chronic inflammatory pathways
- Impairment of muscle repair
- Fibrogenesis and adipogenesis
- Muscular atrophy

HDAC, histone deacetylase.



How DUVYZAT works[2,3]

DUVYZAT is a pan-HDAC inhibitor.

While its exact mechanism of action is unknown, DUVYZAT targets HDAC overactivity.

The DUVYZAT effect[5]

Inhibiting HDAC overactivity with DUVYZAT may lead to increased muscle fiber repair and regeneration, decreased inflammation, and reduced adipogenesis and fibrogenesis.

As the only HDAC inhibitor indicated to treat DMD, DUVYZAT offers a unique, mutation-agnostic approach to protecting muscle function.[1,2,4]

Please see full Important Safety Information on page 19.
Please see full Prescribing Information and Medication Guide in pocket.

Important Safety Information (cont'd)

Warnings and precautions (cont'd)

- Increased Triglycerides: An increase in triglycerides can occur; dosage modification may be needed. Discontinuation may be needed.

DUVYZAT was studied in EPIDYS, one of the largest, most inclusive, phase 3 DMD studies to date[2,*]

EPIDYS was a global, 18-month, double-blind, randomized, placebo-controlled trial[1,2]

179 patients were randomized 2:1 to receive oral DUVYZAT (n=118) or matching placebo (n=61)[1,2]

- Ambulant boys aged ≥6 years with genetically confirmed DMD (median age of 9.8 years)[1,2]
- No restrictions on genetic mutations, but these were generally balanced across both groups[2]
- All patients completed two 4SC assessments with a mean of 8 seconds or less and were ambulatory and able to get up from the floor within 10 seconds[2]
- Patients were on a stable dose and regimen of corticosteroids, which was continued throughout the study[2]

*EPIDYS is an acronym for Epigenetic Rescue of Dystrophin Dysfunction trial.[2]
4SC, 4-stair climb; NSAA, North Star Ambulatory Assessment.

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Primary Endpoint[1]

Change from baseline to month 18 in time to complete 4SC for DUVYZAT compared to placebo[†]

Key Secondary Endpoints[2]

Change from baseline to month 18 in:

- Motor function and muscle strength assessed by the NSAA
- Muscle fat fraction

[My impression is] pretty positive. The idea that we could have a nonsteroidal treatment for DMD that can slow decline in standardized and accepted measures that we use in clinical practice, such as NSAA, is pretty impactful.

– Neuromuscular specialist

[†]The 4SC is a measure of muscle function that tests the time it takes to climb 4 stairs.[1]

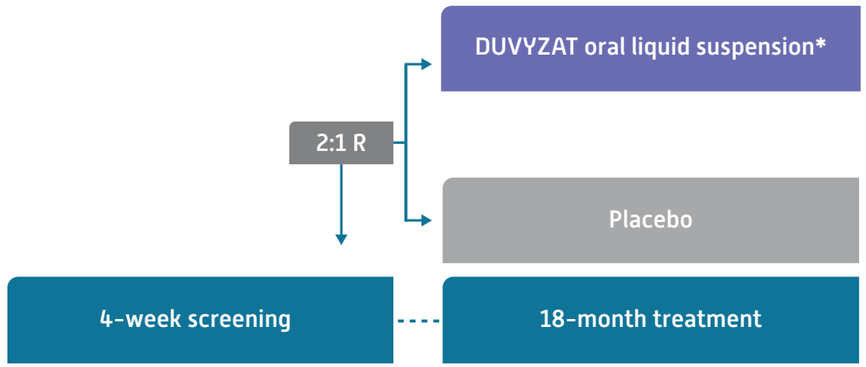
Important Safety Information (cont'd)

Warnings and precautions (cont'd)

- 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.

EPIDYS clinical trial details

179 patients were randomized 2:1 to receive oral DUVYZAT (n=118) or matching placebo (n=61)[1,2]



*Dose adjustments permitted dependent on protocol version at randomization.[1]

The EPIDYS clinical trial also includes an open-label extension phase that is ongoing.[2]

All patients were also receiving systemic corticosteroids.

The 2:1 randomization ratio was chosen because of the rapidly progressive nature of DMD as well as the rarity of the disease. This ratio maximized the number of patients exposed to active treatment while maintaining study integrity.[1,2]

Participants attended study site visits every 12 weeks for 72 weeks

At baseline and at every visit, participants completed[2]:

- ✓ 4SC
- ✓ NSAA, including time-to-rise from the floor
- ✓ Muscle strength assessment (ie, knee extension and elbow flexion, by standardized handheld myometry)

Magnetic resonance spectroscopy (MRS) of the right upper leg was done at screening and after 48 and 72 weeks for the calculation of VLFF.

R, randomization; VLFF, vastus lateralis fat fraction.

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Recruitment was prespecified in 2 groups:

Group A

Baseline VLFF >5% but ≤30%[2]

(Efficacy and safety analysis group, n=120)

Composed of patients who were unlikely to lose mobility suddenly but expected to show measurable decline in function, strength, and fat fraction when on placebo.

Group B

Baseline VLFF ≤5% or >30%[2]

(Safety analysis only, n=59)

Recruited to assess the safety of DUVYZAT in a broader population of patients with DMD.

Ethan, an actual DUVYZAT patient for 4+ years.

Important Safety Information (cont'd)

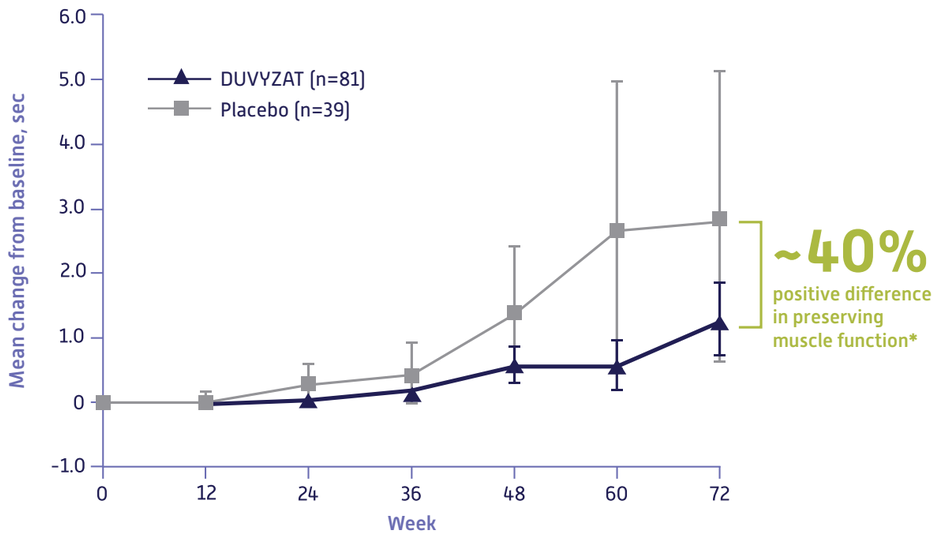
Warnings and precautions (cont'd)

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

PROTECTION against DMD progression with DUVYZAT[1,2,6]

DUVYZAT slowed functional decline by ~40% over 18 months as measured by 4SC

Significantly lower mean change from baseline vs placebo* using 4SC to measure muscle function (*P*=0.037)



Benefit of DUVYZAT over placebo was observed from week 48.[2]

*DUVYZAT or placebo was administered in addition to a stable dose of corticosteroids throughout the study.[1]

Important Safety Information (cont'd)

Recommended Evaluation and Testing Before Initiation of DUVYZAT:
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. Monitor platelet counts and triglycerides as recommended during treatment to determine if dosage modifications are needed.

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Patients treated with DUVYZAT were able to complete 4SC faster than patients taking placebo[1]

Change in time to perform 4SC vs placebo*

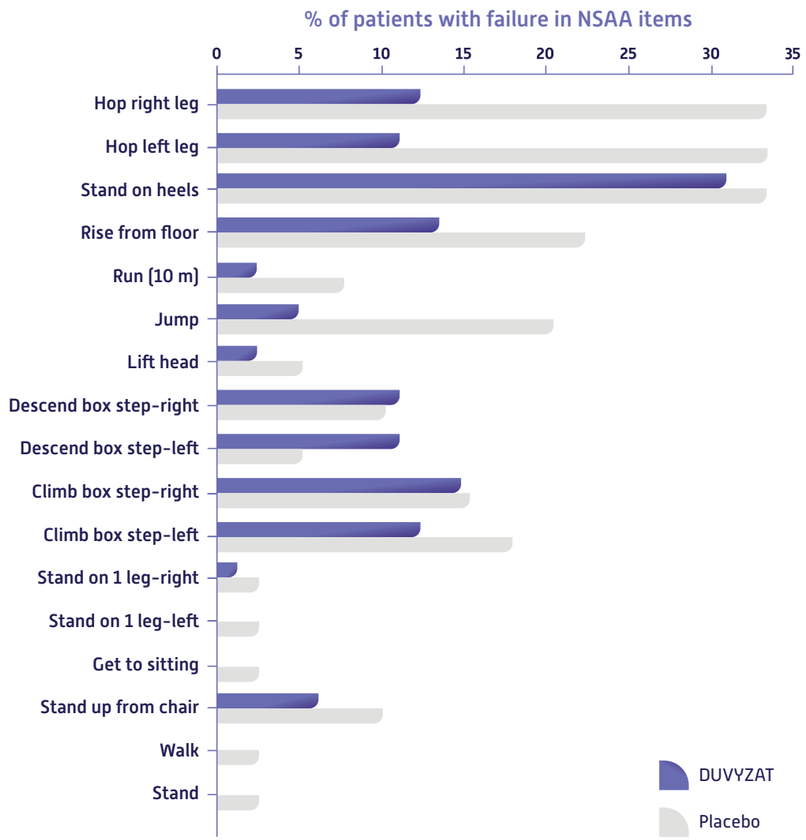
	Mean baseline 4SC (seconds)	Mean change from baseline	Treatment difference from placebo (95% CI)	*P* value
DUVYZAT (n=81)	3.39	1.25	-1.78 (-3.46, -0.11)	0.037
Placebo (n=39)	3.48	3.03		

Ethan, an actual DUVYZAT patient for 4+ years.

Greater preservation of motor function as shown by NSAA[1,2,*]

Fewer failed NSAA test items for patients on DUVYZAT vs placebo[7,*,†]

Loss of NSAA items at 18 months—target population



DUVYZAT offers PROTECTION across multiple measurements of disease progression including 4SC and NSAA.[1,2]

*Nominally significant but not statistically significant based on the prespecified multiplicity adjustment.[2]

†The NSAA is a DMD-specific assessment scale measuring lower limb function in ambulant children with DMD, comprising 17 items scored on a scale of 0 to 2. A score of 2 indicates the activity is performed without difficulty; 1 indicates the activity is performed with some compensation; 0 indicates the activity cannot be performed independently.[1,2,8]

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Slower decline in test items across NSAA vs placebo*,†

Change from baseline in total NSAA item score over 18 months[2]

1.91 points

LESS DECLINE IN MOTOR FUNCTION

Treatment effect: 1.91 (0.30 to 3.53)

DUVYZAT (n=81)
-2.66 (-3.56 to -1.76)

Placebo (n=39)
-4.58 (-5.89 to -3.26)

Important Safety Information (cont'd)

Recommended Evaluation and Testing Before Initiation of DUVYZAT: (cont'd)
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.

Compared with placebo at 18 months,

DUYVZAT reduced new fat infiltration in key muscle groups required for ambulation[1,2,9,*]

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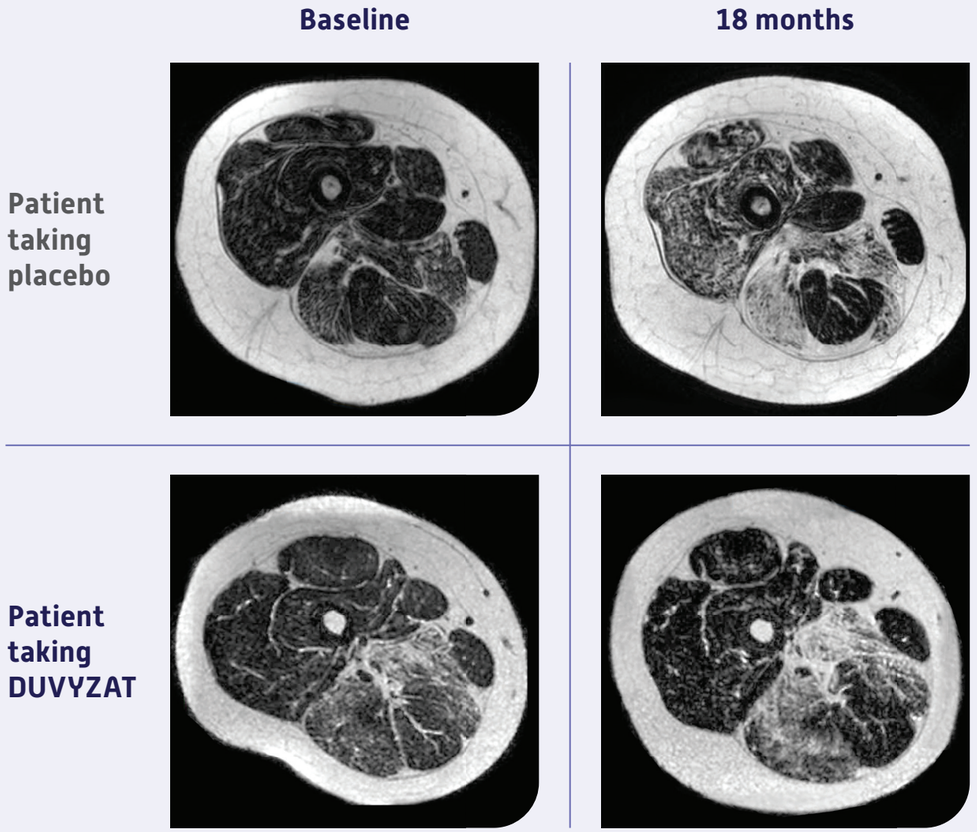
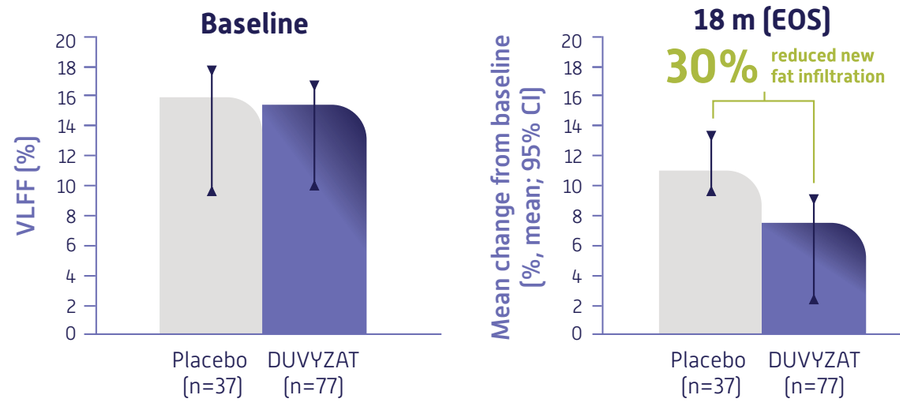
DUVYZAT reduced new fat infiltration in the quadriceps and hamstrings[9]



MRS imaging showing VLFF increase from baseline after 18 months. The difference in fat fraction between the 2 groups is evident.[9,†]

Changes in mean fat fraction over 18 months from baseline[2,9]



At 18 months, for the patients with VLFF baseline in the range of >5% to ≤30%, a mean increase (absolute difference from baseline levels) of VLFF was 7.48% in the DUVYZAT-treated patients compared to a 10.89% increase in patients who received placebo.[1]

*Nominally significant but not statistically significant based on the prespecified multiplicity adjustment.[2]
†MRS imaging from a single patient; may not be representative of all patients.
MRS, magnetic resonance spectroscopy.

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EOS, end of study.

Important Safety Information (cont'd)

Most Common Adverse Reactions:

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

PROTECTION with a well-characterized safety profile[1]

DUVYZAT safety was established across multiple clinical trials including 222 patients, many of whom were treated with DUVYZAT for more than 2 years*

Adverse reactions reported in >5% of DUVYZAT-treated patients and at least 5% greater than placebo in the EPIDYS clinical trial

	DUVYZAT n=118 %	Placebo n=61 %
Diarrhea	37	20
Abdominal pain	34	25
Thrombocytopenia†	33	0
Nausea/vomiting	32	18
Hypertriglyceridemia	23	7
Pyrexia	13	8
Myalgia	9	3
Rash	9	2
Arthralgia	8	2
Fatigue	8	0
Constipation	7	2
Decreased appetite	7	0

*Controlled and uncontrolled trials in patients with confirmed DMD aged 6 years and older treated with DUVYZAT, including 210 patients treated for ≥6 months, 187 patients for ≥12 months, and 105 patients for ≥24 months.[1]

†Thrombocytopenia includes platelet count decreased and thrombocytopenia.[1]

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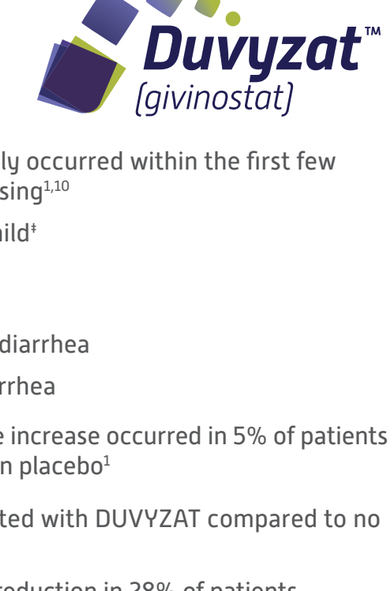
Additional safety information from EPIDYS

Duvyzat™ (givinostat)

- Diarrhea, the most common adverse reaction, usually occurred within the first few weeks of treatment and resolved with continued dosing[1,10]
  - Majority of cases reported were classified as mild‡
    - 3 patients experienced moderate diarrhea
    - 1 patient experienced severe diarrhea
  - 1 patient had interruption in treatment due to diarrhea
  - No patients discontinued treatment due to diarrhea
- Hypothyroidism and/or thyroid-stimulating hormone increase occurred in 5% of patients treated with DUVYZAT compared to 2% of patients on placebo[1]
- Thrombocytopenia occurred in 33% of patients treated with DUVYZAT compared to no patients on placebo[1]
  - Low platelet counts resulted in DUVYZAT dose reduction in 28% of patients
  - 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
- In EPIDYS, 2% of patients on DUVYZAT discontinued due to triglyceride levels >300 mg/dL

95% of patients completed the DUVYZAT clinical trial.[2]



Ryan, an actual DUVYZAT patient for 4+ years.

‡Diarrhea was defined per CTCAE grade: mild=increase of <4 stools per day over baseline; moderate=increase of 4 to 6 stools per day over baseline; severe=increase of ≥7 stools per day over baseline.[10]

CTCAE, Common Terminology Criteria for Adverse Events.

PROTECTION with convenient dosing

DUVYZAT is an oral suspension administered twice daily (can be taken with food)[1]

Initial testing and ongoing monitoring[1]

- Obtain and evaluate baseline platelet counts and triglycerides prior to initiation of DUVYZAT
  - Do not initiate DUVYZAT in patients with a platelet count of <150 x 10^9/L
- In patients with underlying cardiac disease or taking concomitant medications that cause QT prolongation, obtain ECGs:
  - When initiating treatment with DUVYZAT
  - During concomitant use
  - When clinically indicated

After treatment with DUVYZAT has been initiated, ongoing monitoring is required.[1]

Please see full Prescribing Information.

ECG, electrocardiogram ; QTc, heart-rate corrected QT interval.

Important Safety Information

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.

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Weight-based dosing with DUVYZAT[1]

Body weight	Dosage	Oral suspension volume
10 kg to <20 kg	22.2 mg twice daily	2.5 mL twice daily
20 kg to <40 kg	31 mg twice daily	3.5 mL twice daily
40 kg to <60 kg	44.3 mg twice daily	5 mL twice daily
≥60 kg	53.2 mg twice daily	6 mL twice daily

Dose can be modified for adverse reaction mitigation[1]

Modifications may be needed for decreased platelet counts, diarrhea, and increased triglycerides, or QTc prolongation. Please see full Prescribing Information for more details about dosage modifications to mitigate adverse reactions.[1]

	First dosage modification*		Second dosage modification†	
Body weight†	**Dosage**	**Oral suspension volume**	**Dosage**	**Oral suspension volume**
10 kg to <20 kg	17.7 mg twice daily	2 mL twice daily	13.3 mg twice daily	1.5 mL twice daily
20 kg to <40 kg	22.2 mg twice daily	2.5 mL twice daily	17.7 mg twice daily	2 mL twice daily
40 kg to <60 kg	31 mg twice daily	3.5 mL twice daily	26.6 mg twice daily	3 mL twice daily
≥60 kg	39.9 mg twice daily	4.5 mL twice daily	35.4 mg twice daily	4 mL twice daily

*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.

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ITF ARC OFFERS DEDICATED SUPPORT TO HELP MAKE IT EASIER FOR YOUR PATIENTS TO ACCESS THERAPY

ITF ARC offers support that helps make insurance coverage navigation easier, helps address your patients' financial concerns, and encourages adherence to therapy.

ITF ARC can help your patients with:

- Insurance navigation
- Education and adherence support

ITF ARC also offers access solutions for your patients including:

- Copay assistance for eligible commercially insured patients whose health plan covers DUVYZAT
- Education about third-party resources
- Patient assistance program for eligible uninsured and underinsured patients
- Temporary supply programs

Have questions?
Contact a case manager at ITF ARC.

1-855-4 ITF ARC (855-448-3272)
8 AM-8 PM ET, Monday-Friday

To get your patients started today, download the Patient Start Form on DUVYZATHCP.com

Each patient's eligibility for access programs is evaluated on an individual basis. To be eligible, patients must first meet the FDA-approved indication. All programs may be modified or discontinued at any time based on eligibility, state and federal laws, and program availability.

Restrictions apply. See full restrictions for ARC Copay Program, Patient Assistance Program, and temporary supply programs at duvyzathcp.com/ITFARC#

Duvyzat™ (givinostat)

Indication

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

Important Safety Information

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.
- 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.

Recommended Evaluation and Testing Before Initiation of DUVYZAT:

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. 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 initiating treatment with DUVYZAT, during concomitant use, and as clinically indicated.

Most Common Adverse Reactions:

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

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.

Please see full Prescribing Information and Medication Guide in pocket.

PROTECT your patients against DMD progression

Duvyzat™ (givinostat)

PROTECTION for a broad patient population[2-5,*]

Unlike other DMD therapies, DUVYZAT is a mutation-agnostic, nonsteroidal treatment for patients at any stage of their disease.

PROTECTION against DMD progression[1,2]

DUVYZAT demonstrated statistically significant preservation of muscle function as measured by 4SC results and greater preservation of motor function as shown by NSAA scores,[†] compared to placebo.

PROTECTION with a well-characterized safety profile[1]

DUVYZAT safety was established across multiple clinical trials including 222 patients.

PROTECTION with convenient dosing[1]

DUVYZAT offers the convenience of oral dosing, with the flexibility to modify dose as needed.

Visit DUVYZATHCP.com
to learn more and get your patients started today.

*The EPIDYS clinical trial did not include non-ambulatory patients.[2]
[†]Nominally significant but not statistically significant based on the prespecified multiplicity adjustment.[2]

Important Safety Information (cont'd)

Warnings and precautions (cont'd)

- Increased Triglycerides: An increase in triglycerides can occur; dosage modification may be needed. Discontinuation may be needed.

Please see full Important Safety Information on page 19.
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References: 1. DUVYZAT. Prescribing information. ITF Therapeutics; 2024. **2.** Mercuri E, Vilchez JJ, Boespflug-Tanguy O, et al; EPIDYS Study Group. 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. **3.** Consalvi S, Saccone V, Giordani L, Minetti G, Mozzetta C, Puri PL. Histone deacetylase inhibitors in the treatment of muscular dystrophies: epigenetic drugs for genetic diseases. *Mol Med*. 2011;17(5-6):457-465. **4.** Sandonà M, Cavioli G, Renzini A, et al. Histone deacetylases: molecular mechanisms and therapeutic implications for muscular dystrophies. *Int J Mol Sci*. 2023;24(5):4306. **5.** Consalvi S, Mozzetta C, Bettica P, et al. Preclinical studies in the mdx mouse model of duchenne muscular dystrophy with the histone deacetylase inhibitor givinostat. *Mol Med*. 2013;19(1):79-87. **6.** Mercuri EM, Brogna C, Zaidman CM, et al. Givinostat study in DMD: supportive results. Poster presented at: 2024 Muscular Dystrophy Association Clinical & Scientific Conference; March 3-5, 2024; Orlando, FL. **7.** Mercuri E, Brogna C, Mah JK, et al. Givinostat in DMD: results of the Epidys study with particular attention to NSAA. Poster presented at: 2023 World Muscle Society Conference; October 2023; Charleston, SC. **8.** Gupta V, Pitchforth JM, Domingos J, et al. Determining minimal clinically important differences in the North Star Ambulatory Assessment (NSAA) for patients with Duchenne muscular dystrophy. *PLoS One*. 2023;18(4):e0283669. **9.** Vandenborne K. Givinostat in DMD: results of the Epidys study with particular attention to MR measures of muscle fat fraction. Oral presentation at Muscular Dystrophy Association Clinical & Scientific Conference; March 19-22, 2023; Dallas, TX. **10.** Data on file, ITF Therapeutics.

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