CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	217865
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Reviewer Name(s)	Donella Fitzgerald, PharmD
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	March 19, 2024
Subject	Evaluation of the need for a REMS
Established Name	givinostat
Trade Name	Duvyzat
Name of Applicant	Italfarmaco S.p.A.
Therapeutic Class	Histone deacetylase inhibitor
Formulation(s)	8.86 mg/mL oral suspension
Dosing Regimen	Weight based dosing twice daily with food

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

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1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Duvyzat (givinostat) is necessary to ensure the benefits outweigh its risks. Italfarmaco S.p.A (Applicant) submitted a New Drug Application (NDA) 217865 for givinostat with the proposed indication for the treatment of Duchenne muscular dystrophy in patients 6 years of age and older. This application is under review in the Division of Neurology 1 (DN1). The applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Givinostat, a new molecular entity,[a] is a histone deacetylase (HDAC) inhibitor proposed for the treatment of Duchenne muscular dystrophy (DMD) in patients 6 years of age and older. In patients with DMD, excessive and uncontrolled HDAC is associated with inflammation, fibrosis and fatty replacement of muscle fibers. It is hypothesized that givinostat will reduce these symptoms and slow the progression of DMD by inhibiting the HDAC enzymes. Givinostat is proposed as an 8.86 mg/mL oral suspension (equivalent to 10 mg/mL givinostat hydrochloride monohydrate) to be taken chronically[b] twice daily with food. The dosage for givinostat is based on body weight, as outlined in Table 1.

Table 1: Recommended Givinostat Dosing

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

Orphan Drug designation was granted for givinostat on April 12, 2013 and Fast Track designation on August 29, 2016. Givinostat is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for givinostat NDA 217865 relevant to this review:

- 04/12/2013: Orphan drug designation granted
- 08/29/2016: Fast track designation granted
- 09/22/2020: Rare pediatric disease designation granted

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- 04/21/2023: NDA 217865 submission for the treatment of Duchenne muscular dystrophy received
- 11/20/2023: Major amendment acknowledgment letter sent to the applicant;[1] PDUFA goal date extended by 3 months.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

DMD is a rare, incurable X-linked recessive, neuromuscular disorder characterized by progressive muscle degeneration and weakness. The disorder is caused by mutations in the dystrophin gene that decrease the production of dystrophin protein. This leads to a loss of the myofiber membrane integrity with repeated cycles of necrosis and regeneration, causing fibrous connective tissue and fat to progressively replace muscle.[2] Symptoms usually present in early childhood, often exhibiting as delayed motor development. Muscle degeneration worsens throughout childhood and adolescence resulting in the loss of ambulation and wheelchair dependence, decreased respiratory function and ventilator dependence, cardiomyopathy, and death. Patients often die in their late teens to twenties, usually due to cardiac or respiratory failure.[c] DMD primarily affects males and is estimated to occur in approximately 16 live male births per 100,000 in the U.S.[3,d]

3.2. Description of Current Treatment Options

There is no cure for DMD. Glucocorticoids, historically prednisone, are the mainstay of pharmacologic treatment for DMD because of their beneficial effects for improving motor function and pulmonary function, reducing the risk of scoliosis, delaying the loss of ambulation, and possibly for delaying progression of cardiomyopathy and improving survival.[4] Deflazacort and vamorolone are the only systemic corticosteroids with an FDA approved indication for DMD. Prednisone continues to be used for treatment, though an increasing number of clinicians are choosing to initiate glucocorticoid therapy with deflazacort or vamorolone because they offer a more favorable side effect profile than prednisone with regard to weight gain and impact on behavior.[4] There are also targeted antisense oligonucleotide therapies that increase dystrophin expression by exon skipping in patients who have a confirmed amenable gene mutation. Increased dystrophin expression in skeletal muscle is used as a surrogate marker for clinical benefit in these products which include eteplirsen, golodirsen, viltolarsen and casimersen. These products, as well as a recombinant gene therapy treatment, delandistrogene-moxeparvovec-rokl, were granted accelerated approval for treatment of DMD and their clinical trials are

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*
[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

still ongoing. DN1 determined there remains an unmet need for treatments that can provide affected individuals with improved muscle function and lifespan.[5] Additional information regarding FDA approved therapies for DMD are appended to this review (Section 10.1).

4. Benefit Assessment

The pivotal trial (Study 48, NCT 02851797) supporting this application was a Phase 3, multicenter, multinational, randomized, double-blind, placebo controlled, 19-month study to evaluate the efficacy and safety of givinostat in 179 ambulant male subjects (118 givinostat, 61 placebo) ≥ 6 years old with DMD. A weight-based dose regimen was applied, and the dosage of givinostat ranged from 10.6 mg twice daily to 70 mg twice daily. The primary endpoint was the change from baseline to month 18 in 4-stair climb (4SC) time for givinostat compared to placebo. Key secondary endpoints include the following:

- Change from baseline to 18 months in physical function
- Time to rise from floor
- Distance walked in 6 minutes using six-minute walking test
- Muscle strength evaluated by knee extension and elbow flexion
- Fat fraction of vastus lateralis muscles

The Applicant reported that the primary endpoint for Study 48 was met, as patients treated with givinostat show statistically significant (p=0.037) less decline in the 4SC compared to placebo. The mean 4SC increased by 1.25 seconds in the givinostat group vs 3.03 seconds in the placebo group. The secondary endpoints all favored treatment with givinostat, although they did not reach statistical significance. The medical officer concluded that there is substantial evidence of effectiveness for givinostat for DMD as the primary endpoint was met in the single pivotal adequate and well-controlled clinical trial.[6]

5. Risk Assessment & Safe-Use Conditions

The primary safety analysis consists of data from the 179 subjects who participated in the pivotal Phase 3 trial. No deaths were reported during the trial. Serious adverse events (SAEs) were reported in 6.8% (8) of givinostat patients compared to 3.3% (2) for placebo. The SAE are outlined below in Table 2.

Table 2: Patients with SAEs by System Organ Class and Preferred Term – Trial 48[6]

System Organ Class Preferred Term	Givinostat N=118 n (%)	Placebo N=61 n (%)	Givinostat vs. Placebo Risk Difference (%) (95% CI)
Any SAE	8 (6.8)	2 (3.3)	3.5 (-2.9, 9.9)
Gastrointestinal disorders (SOC)	2 (1.7)	0	1.7 (-0.6, 4.0)
Abdominal pain	1 (0.8)	0	0.8 (-0.8, 2.5)
Vomiting	1 (0.8)	0	0.8 (-0.8, 2.5)
General disorders and administration site conditions (SOC)	1 (0.8)	0	0.8 (-0.8, 2.5)
Chest pain	1 (0.8)	0	0.8 (-0.8, 2.5)
Infections and infestations (SOC)	3 (2.5)	2 (3.3)	-0.7 (-6.0, 4.6)
Gastroenteritis viral	1 (0.8)	0	0.8 (-0.8, 2.5)
Influenza	1 (0.8)	0	0.8 (-0.8, 2.5)
Gastroenteritis	1 (0.8)	2 (3.3)	-2.4 (-7.2, 2.3)

System Organ Class Preferred Term	Givinostat N=118 n (%)	Placebo N=61 n (%)	Givinostat vs. Placebo Risk Difference (%) (95% CI)
Injury, poisoning and procedural complications (SOC)	1 (0.8)	0	0.8 (-0.8, 2.5)
Spinal fracture	1 (0.8)	0	0.8 (-0.8, 2.5)
Nervous system disorders (SOC)	1 (0.8)	0	0.8 (-0.8, 2.5)
Dizziness	1 (0.8)	0	0.8 (-0.8, 2.5)
Skin and subcutaneous tissue disorders (SOC)	1 (0.8)	0	0.8 (-0.8, 2.5)
Rash	1 (0.8)	0	0.8 (-0.8, 2.5)

None of the SAEs resulted in study drop out. Treatment emergent adverse events (AEs) leading to treatment discontinuation occurred in givinostat subjects only. They included diarrhea (1.7%), abdominal pain (0.8%), increased blood triglycerides (0.8%) and hypertriglyceridemia (1.7%).

5.1. Hypertriglyceridemia

Hypertriglyceridemia was a common adverse event reported in the givinostat pivotal trial. Fifty-eight (23%) subjects in the givinostat treatment group and 4 (7%) subjects in the placebo group experienced elevated triglyceride levels. Most of the events were mild to moderate in severity; one was severe. None of the triglyceride elevations reached levels that are associated with increased risk of acute pancreatitis (1000 mg/dL).[6] Dose modification due to elevated triglycerides occurred in 8% of givinostat subjects and study discontinuation occurred in 3% of the subjects taking givinostat. The Applicant reported that the triglyceride increases were reversible with interruption or discontinuation of givinostat treatment.[6] The proposed Prescribing Information for givinostat has a Warning and Precaution for increased triglycerides and includes monitoring instructions. Labeling will include to monitor triglycerides at 1 month, 3 months, 6 months, and then every 6 months thereafter. Recommendations regarding the need for treatment interruption and dose adjustment are also included.

5.2. Thrombocytopenia

Drug induced thrombocytopenia is a dose-limiting toxicity of the HDAC inhibitor drug class.[7] Thrombocytopenia was among the most frequently reported adverse events in Study 48. Table 3 shows the number of patients in Study 48 that experienced a reduction in platelets.

Table 3. Adverse Events of Special Interest Assessment, Platelet Reduction – Study 48[6]

Platelet Reduction Assessment	Givinostat N=118 n (%)	Placebo N=61 n (%)	Givinostat vs. Placebo Risk Difference (%) (95% CI)
AE grouping related to AESI	39 (33.1)	0	33.1 (24.6, 41.5) *
Platelet count decreased	22 (18.6)	0	18.6 (11.6, 25.7) *
Thrombocytopenia	19 (16.1)	0	16.1 (9.5, 22.7) *
Maximum severity			
Death	0	0	0 (0, 0)
Life-threatening	0	0	0 (0, 0)
Severe	0	0	0 (0, 0)
Moderate	5 (4.2)	0	4.2 (0.6, 7.9) *
Mild	34 (28.8)	0	28.8 (20.6, 37.0) *

Platelet Reduction Assessment	Givinostat N=118 n (%)	Placebo N=61 n (%)	Givinostat vs. Placebo Risk Difference (%) (95% CI)
Serious	0	0	0 (0, 0)
Deaths	0	0	0 (0, 0)
Resulting in discontinuation	0	0	0 (0, 0)
Relatedness	38 (32.2)	0	32.2 (23.8, 40.6) *

Source: adae.xpt; Software: R
Asterisk (*) indicates that 95% confidence interval excludes zero.
Treatment-emergent adverse events defined as an AE that started or worsened on or after the date of start of the administration of the IMP.
Duration is 18-month double-blind treatment period.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Relatedness is determined by investigator.
Abbreviations: AE, adverse event; AESI, adverse events of special interest; CI, confidence interval; IMP, investigational medicinal product; N, number of patients in treatment arm; n, number of patients with adverse event

Six subjects had a platelet value below 100 x 10^9/L during the Study, with the lowest count being 60 x 10^9/L. The majority of the thrombocytopenia incidents were mild. No serious clinical bleeding events occurred in the trial, however givinostat subjects did report contusions (5.1%), epistaxis (2.5%), hematoma (1.7%) and anal bleeding due to constipation (0.8%).[6] DN1's draft Integrated Review for givinostat states that thrombocytopenia was dose-related and reversible upon treatment discontinuation. The proposed Prescribing Information for givinostat includes a Warning and Precaution for hematological changes which states that the study drug is associated with decreased blood cell counts, most prominently, platelet counts. Monitoring, dose adjustment and treatment discontinuation instructions are also included in the draft label. Labeling will include to monitor blood counts every 2 weeks for the first 2 months of treatment, then monthly for the first 3 months, and every 3 months thereafter. Dose modification is recommended for incidents of confirmed thrombocytopenia and treatment should be discontinued if thrombocytopenia worsens despite decreasing the dose. To better characterize the incidence, frequency, and severity of thrombocytopenia in the postmarketing setting, DN1 has determined that a postmarketing requirement (PMR) will be required. Additionally, the applicant will be requested to conduct enhanced pharmacovigilance for thrombocytopenia.

5.3. QT Prolongation

The risk of QT prolongation was not observed in the givinostat Phase 3 clinical trial, however, QTcF prolongation was detected in a separate Thorough QT study[8]of moxifloxacin and givinostat at therapeutic (100 mg) and supratherapeutic (300 mg) doses conducted by the applicant. Per the Agency's Interdisciplinary Review Team for Cardiac Safety Studies, the study data did not show that the 100 mg dose was associated with significant QTc prolonging effect, but the 300 mg dose was associated with QT prolongation. Based on the results of this study and literature reports that HDAC inhibitors have been associated with delayed cardiac repolarization and arrhythmias[9], draft labeling includes a Warning and Precaution stating that givinostat can cause prolongation of QTc interval and to avoid use of givinostat in patients at increased risk for ventricular arrhythmias. Additionally, in the Drug Interactions section of the draft label, healthcare providers are instructed to avoid concomitant use with other drugs that prolong the QTc interval and to monitor ECG if concomitant use cannot be avoided.

6. Expected Postmarket Use

Givinostat is proposed as an oral suspension and will be administered in both inpatient and outpatient settings. In the outpatient setting, DMD patients often have caregivers who administer medications since it is a largely pediatric population and affected patients may have significant physical disability. Though the medical care team for a patient with DMD is typically managed by a multidisciplinary team, it is expected that givinostat will be prescribed by specialists, with neurologists being the most likely prescribers. These clinicians will likely have experience treating patients with DMD and would be capable of incorporating routine laboratory monitoring for hypertriglyceridemia and thrombocytopenia as part of the patient's treatment plan.[10]

In the outpatient setting, patients will need to adhere to the recommendations for hematological and triglyceride monitoring. They will also need to report any signs or symptoms to their prescriber that may be indicative of thrombocytopenia (e.g., bruising or bleeding), as well as the heart palpitations, chest pain, shortness of breath or lightheadedness that can be associated with QT prolongation.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for givinostat beyond routine pharmacovigilance and labeling. Draft labeling includes a Medication Guide for patients that includes language regarding hypertriglyceridemia and thrombocytopenia.

8. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of givinostat on the basis of the efficacy and safety information currently available.[6]

DMD is a rare, incurable X-linked recessive, neuromuscular disorder characterized by progressive muscle degeneration and weakness that ultimately leads to loss of ambulation, decreased respiratory function and ventilator dependence, cardiomyopathy, and death. DMD primarily affects males and is estimated to occur in approximately 16 live male births per 100,000 in the U.S. There is no cure for DMD, however, there are seven FDA-approved treatments. Four of the treatments are targeted antisense oligonucleotide therapies (eteplirsen, golodirsen, viltolarsen, casimersen), one is a recombinant gene therapy (delandistrogene-moxeparvovec-rokl) and two are corticosteroids (deflazacort, vamorolone).

Efficacy of givinostat was demonstrated in a single pivotal trial by meeting the primary endpoint of reduction in the decline in 4SC compared to placebo. In the Phase 3 trial for givinostat the risks of hypertriglyceridemia and thrombocytopenia were identified through routine monitoring, most were mild to moderate in severity and resolved with dose modifications or treatment interruption. Draft labeling includes Warnings and Precautions for hypertriglyceridemia and thrombocytopenia, it provides recommendations about the frequency to monitor for these events and the need to reduce the dose or discontinue givinostat to prevent worsening and resolve events. Draft labeling also includes a Medication Guide for patients that includes information about the risks of hypertriglyceridemia and thrombocytopenia and what to do if they experience any signs or symptoms. Additionally, DN1 intends to issue a PMR and request enhanced pharmacovigilance to

gain additional information about the risk of thrombocytopenia in a larger patient population. The risk of QT prolongation was not observed in the Phase 3 clinical trial, however, QTcF prolongation was detected in a separate QT study conducted by the applicant. Due to this finding and reports in literature of delayed cardiac repolarization and arrythmias with HDAC inhibitor treatment, draft labeling will warn prescribers to avoid givinostat use in patients with an increased risk of ventricular arrhythmias or other significant cardiac disease.

The healthcare providers who are expected to prescribe givinostat will likely be specialists and are typically followed by a healthcare team with experience in treating complex conditions such as DMD where patients are followed closely by their providers. These prescribers would understand the importance of avoiding givinostat use in patients with cardiac issues and should be capable of providing routine laboratory monitoring for hypertriglyceridemia and thrombocytopenia as part of the patient's treatment plan. Therefore, based on the data currently available, this reviewer is not recommending a REMS for the management of the risks associated with givinostat therapy.

9. Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks. The safety concerns observed with givinostat are monitorable and manageable with dose adjustments or treatment interruptions. In general, healthcare providers who treat DMD are familiar with managing a complex disease and understand the importance of regular patient monitoring.

Should DN1 have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

Appendices

9.1. FDA Approved Therapies for the Treatment of DMD[11]

Drug (Approval Date)	Indication	Dosing and Administration	Important Safety & Tolerability Issues	Risk Management Approaches
Exondys 51 - eteplirsen (09/19/2016)	Treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping	30 mg/kg IV once weekly	Hypersensitivity reactions	Labeling – Warnings & Precautions
Emflaza – Deflazacort (02/09/2017)	Treatment of DMD in patients ≥ 2 years of age	0.9 mg/kg once daily	Adrenal suppression Immunosuppression Thyroid disease Cardiovascular disease Gastrointestinal disease Psychiatric disturbances Osteoporosis Kaposi Sarcoma Thromboembolic events	Labeling – Warnings & Precautions
Vyondys 53 – golodirsen (12/12/2019)	Treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping	30 mg/kg IV once weekly	Hypersensitivity reactions Renal toxicity	Labeling – Warnings & Precautions
Viltepso – viltolarsen (b) (4)	Treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping	80 mg/kg by IV infusion once weekly	Renal toxicity	Labeling – Warnings & Precautions
Amondys 45 – casimersen (02/25/2021)	Treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping	100 mg/2mL by IV infusion once weekly	Hypersensitivity reactions Renal toxicity	Labeling – Warnings & Precautions
Elevidys-delandistrogene-moxeparvovec-rokl (06/22/2023)	Treatment of DMD in ambulatory pediatric patients aged 4-5 years with a confirmed mutation in the DMD gene	$1.33x10^{14}$ vector genomes per kg of body weight	Hepatotoxicity Myositis Myocarditis	Labeling – Warnings & Precautions
Agamree-vamorolone (10/26/23)	Treatment of DMD in patients 2 years of age and older	6 mg/kg once daily, up to a maximum daily dosage of 300 mg for patients > 50 kg	Endocrine dysfunction Immunosuppression Cardiovascular/Renal dysfunction GI perforation	Labeling – Warnings & Precautions

9.2. References

[1] Freilich E. Division of Neurology 1 Major Amendment Acknowledgement Letter for Givinostat, NDA 217865, dated November 20, 2023.

[2] Darras BT. Duchenne and Becker muscular dystrophy: Glucocorticoid and disease-modifying treatment. *UpToDate*. September 1, 2020.

[3] 3 Duchenne muscular dystrophy. National Center for Advancing Translational Sciences. Genetic and Rare Diseases Information Center. https://rarediseases.info.nih.gov/diseases/6291/d chenne-muscular-dystrophy. Published November 2, 2020. Accessed October 1, 2023.

[4] Darras BT. Duchenne and Becker muscular dystrophy: Glucocorticoid and disease-modifying treatment. *UpToDate*. September 1, 2020.

[5] Division of Neurology 1. Draft Integrated Review for Givinostat, NDA 217865, March 14, 2024.

[6] Italfarmaco S.p.A. Clinical Overview for Givinostat, NDA 217865, April 21, 2023.

[7] Ali A, Bluteau O, Messaoudi K, Palazzo A, et al. Thrombocytopenia induced by the histone deacetylase inhibitor abexinostat involves p53-dependent and -independent mechanisms. Cell Death Dis. 2013 Jul 25;4(7):e738. doi: 10.1038/cddis.2013.260. PMID: 23887629; PMCID: PMC3730430.

[8] Italfarmaco S.p.A. A Randomized, Partially Double-Blind, Four-Period, Four Treatment, Crossover Study Investigating the Placebo-Corrected Effects of a Therapeutic Dose (100 mg) and a Supratherapeutic Dose (300 mg) of Givinostat and Moxifloxacin on QT/QTc Interval in Healthy Male and Female Subjects.

[9] Spence S, Deurinck M, et al. Histone deacetylase inhibitors prolong cardiac repolarization through transcriptional mechanisms. Toxicol Sci. 2016 Sep;153(1):39-54.

[10] Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, Cripe L, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol. 2010 Jan. 9 (1):77-93

[11] Darras BT. Duchenne and Becker muscular dystrophy: Glucocorticoid and disease-modifying treatment. *UpToDate*. September 1, 2020 and Chapman I. Division of Risk Management. REMS Review for casimersen, NDA 213026. February 16, 2021.

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