EU Risk Management Plan for DUVYZAT oral suspension (Givinostat)

RMP version to be assessed as part of this application:

RMP Version number: version 1.0

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Rationale for submitting an updated RMP: RMP version 1.0 finalisation

Summary of significant changes in this RMP: Amendments in Part IV, Part VI and Part VII

QPPV name: Mirko Fedrigo

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant´s QPPV.
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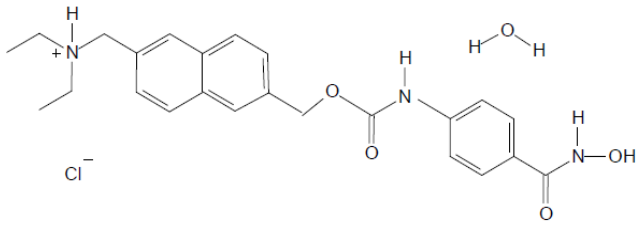
Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Givinostat hydrochloride monohydrate
Pharmacotherapeutic group(s) (ATC Code)	Other drugs for disorders of the musculo-skeletal system (M09; ATC code: M09AX14).
Marketing Authorisation Applicant	Italfarmaco S.p.A.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Duvyzat 8.86mg/mL oral suspension
Marketing authorisation procedure	Centralised Procedure
Brief description of the product	Chemical class Agents that inhibit HDAC activity vary in structure. Givinostat hydrochloride monohydrate (Givinostat) is an *N*,hydroxy-benzamide derivative. Chemical name: Diethyl-[6-(4-hydroxycarbamoyl-phenyl carbamoyloxymethyl)-naphthalen-2-ylmethyl]-ammonium; chloride; monohydrate. 

	Summary of mode of action Zinc ion dependent histone deacetylases (HDACs) are a class of 11 isoenzymes associated with numerous nuclear repressor complexes that, once recruited to specific sites of euchromatin, maintain nucleosome histones in a state of deacetylation so that DNA remains tightly bound and inaccessible to transcription factors for gene expression. In contrast, inhibition of HDAC results in hyperacetylation of these histones and allows the unravelling of DNA sufficient for the binding of transcription factors and the synthesis of mRNA. DUVYZAT (Givinostat), an orally active hydroxamic acid derivative, is a potent fast-on, fast-off competitive inhibitor that binds to the active site of the HDAC isoforms impeding substrate access. Several studies demonstrated that Givinostat is a pan-HDAC inhibitor with IC_{50} values below 120 nM for class I and class IIb isoforms. Givinostat can also inhibit the specific class IIa enzymatic activity, although with lower potency. Duchenne Muscular Dystrophy (DMD) is caused by mutations in the dystrophin gene leading to dystrophin deficiency, muscle fibre degeneration and progressive fibrotic and fatty replacement of muscles. Pharmacological blockade of the histone deacetylase activity, which is constitutively active in DMD muscles by HDAC inhibitors (HDACi), prevents fibrosis and promotes compensatory regeneration in the mdx mouse, a model of DMD. Givinostat is a potent HDACi currently being developed for the treatment of DMD. In mdx mice, Givinostat dose and concentration dependently increased the cross-sectional area of myofibers, decreased the cellular inflammatory infiltrate and prevented the formation of fibrotic scars. These findings strongly suggested that in this DMD animal model Givinostat was able to inhibit all the processes, which determine muscle fibrotic substitution (inflammation, necrosis, fatty replacement and fibrosis), and to stimulate muscle regeneration with the formation of larger muscle fibres and overall, more muscle tissue. Results also suggested that exposures of Givinostat of 300 ng*h/mL are required to exert the beneficial effect. Clinical findings showed that administration of Givinostat for more than one year significantly counteracts histological disease progression in ambulant DMD boys aged seven to ten years [**Bettica P, 2016**]
	Important information about its composition None. Givinostat is manufactured by chemical synthesis.
Hyperlink to the Product Information	The product information including the SmPC and the PIL is included in Module 1.3.1 of the eCTD
Indication(s) in the EEA	Current: Duvyzat is indicated for the treatment of Duchenne muscular dystrophy (DMD) in ambulant patients, aged 6 years and older, and with concomitant corticosteroid treatment.

<table>
<tr><td></td><td>Proposed (if applicable):</td></tr>
<tr><td>Dosage in the EEA</td><td>Current: The recommended dose of Duvyzat is based on body weight and should be administered orally twice daily (see Table 1).

Table 1 – Recommended Dosage
<table><tr><th>Weight[a]</th><th>Dosage</th><th>Oral Suspension Volume</th></tr><tr><td>15 kg to less than 20 kg</td><td>22.2 mg twice daily</td><td>2.5 mL twice daily</td></tr><tr><td>20 kg to less than 40 kg</td><td>31 mg twice daily</td><td>3.5 mL twice daily</td></tr><tr><td>40 kg to less than 60 kg</td><td>44.3 mg twice daily</td><td>5 mL twice daily</td></tr><tr><td>60 kg or more</td><td>53.2 mg twice daily</td><td>6 mL twice daily</td></tr></table>[a] Based on actual body weight

The decision to continue treatment in patients who become non-ambulatory should be taken at the discretion of the physician based on the overall benefit and risk assessment.

Dose adjustment for thrombocytopenia, diarrhoea or hypertriglyceridaemia

A dose reduction (see Table 2) should be applied for patient with:
• Platelet count < 150 x 10^9/L verified by two assessments one week apart,
or
• Moderate or severe diarrhoea (more than 4 stools per day),
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
<table><tr><th></th><th colspan="2">First Dosage Modification[b]</th><th colspan="2">Second Dosage Modification[c]</th></tr><tr><th>Weight[a]</th><th>Dosage</th><th>Oral Suspension Volume</th><th>Dosage</th><th>Oral Suspension Volume</th></tr><tr><td>15 kg to less than 20 kg</td><td>17.7 mg twice daily</td><td>2 mL twice daily</td><td>13.3 mg twice daily</td><td>1.5 mL twice daily</td></tr><tr><td>20 kg to less than 40 kg</td><td>22.2 mg twice daily</td><td>2.5 mL twice daily</td><td>17.7 mg twice daily</td><td>2 mL twice daily</td></tr><tr><td>40 kg to less than 60 kg</td><td>31 mg twice daily</td><td>3.5 mL twice daily</td><td>26.6 mg twice daily</td><td>3 mL twice daily</td></tr><tr><td>60 kg or more</td><td>39.9 mg twice daily</td><td>4.5 mL twice daily</td><td>35.4 mg twice daily</td><td>4 mL twice daily</td></tr></table>[a] Based on actual body weight</td></tr>
</table>

	[b] If the adverse reaction(s) persist after the first dosage modification, proceed to the second dosage modification. [c] If the adverse reaction(s) persist after the second dosage modification, Duvyzat should be discontinued.
	Proposed (if applicable): Not applicable.
Pharmaceutical form(s) and strengths	Current (if applicable): Oral suspension (White to off-white or faintly pink, homogenous suspension when mixed). DUVYZAT oral suspension (Givinostat) is available in an amber polyethylene terephthalate bottle containing 140 mL oral suspension closed with a high-density polyethylene child-resistant closure with low-density polyethylene syringe adapter. Each pack contains one bottle and one graduated oral syringe of 5 mL. The syringe of 5 mL is graduated from 1 to 5 mL by increments of 0.5 mL
	Proposed (if applicable): Not applicable.
Is/will the product be subject to additional monitoring in the EU?	Yes.

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Duchenne Muscular Dystrophy (DMD)

Duchenne Muscular Dystrophy (DMD) is a rare disorder caused by mutations in the dystrophin gene.

Incidence: DMD primarily affects males with an estimated incidence of 1/3,300 male births. Females are usually asymptomatic, but a small percentage of female carriers manifest milder forms of the disease (symptomatic form of muscular dystrophy of Duchenne and Becker in female carriers) [**Orphanet, 2021**].

Prevalence: Birth prevalence was reported as 15.9 per 100,000 new-born males in the USA and 19.5 per 100,000 new-born males in UK and Wales. A worldwide network for neuromuscular diseases, which supports new therapies for patients, calculated the point prevalence. For France, USA, UK and Canada the point prevalence of DMD was calculated as 10.9, 1.9, 2.2 and 6.1 per 100,000 males, respectively [**Ryder S, 2017**].

In a recent meta-analysis, the pooled global DMD prevalence was 7.1 cases (95% CI: 5.0-10.1) per 100,000 males and 2.8 cases (95% CI: 1.6-4.6) per 100,000 in the general population, while the pooled global DMD birth prevalence was 19.8 (95% CI:16.6-23.6) per 100,000 live male births [**Crisafulli S, 2020**].

Several studies indicate that prognosis for survival in DMD has improved in recent decades. Median life expectancy with ventilatory support, introduced in most settings in the 1990s, ranged between 21.0 and 39.6 years (pooled median: 29.9 years, 26.5-30.8; weighted pooled median: 31.8 years, 29.3-36.2) [**Landfeldt E, 2020**]. Other recent analyses stratified by 3 time periods in which patients were born showed markedly increased life expectancy in more recent patient populations; patients born after 1990 have a median life expectancy of 28.1 years (95% CI 25.1, 30.3) [**Broomfield J, 2021**].

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease

DMD is an X-linked recessive inherited neuromuscular disorder due to mutations in the dystrophin gene. It is characterized by progressive muscle weakness and wasting due to the absence of dystrophin protein that causes degeneration of skeletal and cardiac muscle. The molecular diagnostic of DMD involves a deletions/duplications analysis performed by quantitative technique such as microarray-based comparative genomic hybridization (array-CGH), Multiple Ligation Probe Assay MLPA [**Falzarano MS; 2015**]. Age of onset is usually between 3 and 5 years of age (see: https://rarediseases.org/rare-diseases/duchenne-muscular-dystrophy/#:~:text=Age%20of%20onset%20is%20usually,individuals%20in%20the%20United%20States, accessed November 29, 2022).

Due to the localization of the dystrophin gene on the X chromosome, DMD predominantly affects male children, while females are likely to be asymptomatic "healthy carriers" [**Crisafulli S, 2020**].

There are 3 main risk factors associated with poor outcome in patients with DMD. These are low body mass index (BMI), poor lung function, and high cardiac biomarkers like *N*-terminal pro-brain natriuretic peptide [**Cheeran D, 2017**].

The main existing treatment options:

Duchenne Muscular Dystrophy

Physiotherapy and treatment with glucocorticoids remain the mainstays of DMD treatment and should continue after loss of ambulation. Glucocorticoids have become standard of care in many countries based on evidence that prednisolone and deflazacort can prolong the ambulant stage.

Early use of cardioprotective agents, non-invasive positive pressure ventilation, and other supportive strategies has improved the life expectancy and health-related quality of life for many young adults with DMD. New emerging treatment includes viral-mediated microdystrophin gene replacement, exon skipping to restore the reading frame, and nonsense suppression therapy to allow translation and production of a modified dystrophin protein. Other potential therapeutic targets involve upregulation of compensatory proteins, reduction of the inflammatory cascade, and enhancement of muscle regeneration [**Mah JK, 2016**].

In August 2014, ataluren was granted conditional marketing authorisation by the European Commission for use in the European Union, targeting the approximately 11% of boys with DMD caused by a stop codon in the dystrophin gene [**Birnkrant D, 2018**]. The approval has subsequently been extended to ambulatory patients aged 2 years and older. Ataluren interferes with the ribosomal translational machinery in such a way that premature nonsense stop codons in the mRNA are read through by the translational machinery; this results in the translation of the entire mRNA and hence production of a full-length dystrophin protein product and hence restoration of its function in muscle cells.

Another promising approach for treating DMD is gene transfer to restore dystrophin expression using a safe, non-pathogenic viral vector called adeno-associated viral (AAV) vector. Whilst microdystrophin gene transfer using AAV vectors shows extremely impressive therapeutic success so far in large animal models of DMD, translating this advanced therapy medicinal product from bench to bedside still offers scope for many optimization steps. These treatment strategies may apply to a subset of DMD patients depending on the mutations they carry [**Elangkovan G, 2021**].

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Duchenne Muscular Dystrophy

Duchenne muscular dystrophy is the most common form of muscular dystrophy in childhood. It is caused by mutations of the *DMD* gene, Disease progression is characterized by increasing muscle necrosis, fibrosis, and fatty tissue replacement and a greater degree of fibre size variation seen in subsequent muscle biopsies. This leads to progressive muscle weakness, loss of independent ambulation by early teens, and premature death due to cardiorespiratory complications [**Mah JK, 2016**].

A multi-centre retrospective cohort study of 408 males with DMD, followed from January 1, 2005 to December 31, 2015, was conducted to identify risk factors for death. Those dying of cardiac causes were compared to those dying of non-cardiac causes and to those alive at study end. There were 29 (7.1%) deaths at a median age of 19.5 (IQR: 16.9-24.6) years; 8 (27.6%) cardiac, and 21 (72,4%) non-cardiac. Those living were younger [14.9 (IQR: 11.0-19.1) years] than those dying of cardiac [18 (IQR 15.5-24) years, p = 0.03] and non-cardiac [19 (IQR: 16.5-23) years, p = 0.002] causes. GC use was lower for those dying of cardiac causes compared to those living [2/8 (25%) vs. 304/378 (80.4%), p = 0.001]. Last ejection fraction prior to death/study end was lower for those dying of cardiac causes compared to those living (37.5% ± 12.8 vs. 54.5% ± 10.8, p = 0.01) but not compared to those dying of non-cardiac causes (37.5% ± 12.8 vs. 41.2% ± 19.3, p = 0.58). In a large DMD cohort, approximately 30% of deaths were cardiac. Lack of GC use was associated with cardiac causes of death, while systolic dysfunction was associated with death from any cause [**Wittlieb-Weber CA, 2020**].

Important co-morbidities:

Duchenne Muscular Dystrophy

The muscles of the chest wall and abdomen are gradually affected, particularly after loss of ambulation. Inactivity, slumped posture, overweight and scoliosis contribute further to chronic hypoventilation and a reduced ability to cough. There should be a low threshold for use of antibiotics in respiratory tract infections. Oxygen therapy should be used with caution, as this can seemingly improve hypoxia but mask underlying causes such as atelectasis or hypoventilation, and lead to decreased respiratory drive and worsen hypercapnia in cases of chronic hypoventilation.

The most common forms of heart disease in Duchenne muscular dystrophy are dilated cardiomyopathy and/or arrhythmia. Remodelling of cardiac muscle tissue with areas characterised by atrophy, hypertrophy and myocardial fibrosis has been documented.

Several studies have shown reduced bone mineral content in patients with Duchenne muscular dystrophy as assessed by dual-energy X-ray, and prolonged glucocorticoid therapy seems to exacerbate this tendency. Some studies have shown an increased risk of osteoporotic vertebral fractures when patients are treated with glucocorticoids.

Around one third of patients with Duchenne muscular dystrophy have cognitive difficulties. Average IQ is one standard deviation lower than in healthy boys. This cognitive impairment is not progressive. There is an increased incidence of ADHD, autism spectrum disorders, obsessive-compulsive traits and specific language, reading and learning disabilities [**Annexstad EJ, 2014**].

Part II: Module SII - Non-clinical part of the safety specification

Key safety findings from non-clinical studies and relevance to human usage:

Toxicity

- key issues identified from acute or repeated-dose toxicity studies

  Single-dose toxicity data

  Acute toxicity of Givinostat was assessed in the mouse and in the rat, following IV and oral administration. Results are summarized in the table below:

Table 1 - Summary of Single-Dose Toxicity Studies

Species	Route	Dose	Results
CD-1 Mouse	Oral	1000 mg/kg	LD_{50} > 1000 mg/kg
CD-1 Mouse	IV	Up to 200 mg/kg	LD_{50} = 152 mg/kg
Sprague Dawley Rat	Oral	Up to 5000 mg/kg	LD_{50} between 2400 and 5000 mg/kg
Sprague Dawley Rat	IV	Up to 150 mg/kg	LD_{50} = 132 mg/kg

Following IV treatment, deaths occurred shortly after treatment (30-60 seconds) in the mouse and within 30 minutes in the rat, at all doses except for the lowest dose in both species. Treatment-related clinical signs observed in surviving animals included shallow/difficult breathing, hypoactivity, tremors or clonic convulsion in both rodent species, particularly at the highest doses. After oral treatment, death occurred between 32 and 40 hours after administration in one mouse and between 48 hours and 9 days in the rat. Less severe clinical sings were observed after oral administration (compared to the IV route), represented by slight hypokinesia in the mouse, piloerection, hunched posture, diarrhea, shallow breathing and hypoactivity in the rat, mainly limited to animals given the higher doses.

Relevance to human usage: None, because the doses used were much higher than the proposed therapeutic range.

Repeated-dose toxicity data

Repeated-dose toxicity studies were carried out in four different animal species (mouse, rat, dog, and monkey), with evaluation of toxicokinetic (TK) parameters.

A 13-week oral toxicity study was carried out in the CD-1 mouse, where Givinostat was administered once daily by oral gavage, at doses of 50, 100 and 200 mg/kg/day. Based on incidence and severity of observed findings, the identified NOAEL in this study was 100 mg/kg/day.

Repeated-dose toxicity studies of different duration (4-, 13- and 26-week) were conducted in the Sprague Dawley rat. Givinostat was administered once daily by the oral (gavage) route. In the 4-week oral toxicity study, Givinostat was in general well tolerated at all tested doses (50, 125 and 250 mg/kg/day), with treatment-related effects mainly limited to animals receiving the high and the intermediate dose. Based on the observed findings, the NOAEL in this study was 50 mg/kg/day. In the 13-week oral toxicity study Givinostat was administered at 10, 40 and 160 mg/kg/day. Changes observed at 160 mg/kg/day indicated that this dose exceeded the MTD, whereas Givinostat was well-tolerated at lower doses. Changes observed at 10 mg/kg/day were of minimal severity and this dose was considered as NOAEL in this study.
Comparable results were observed in the 26-week oral toxicity study, where Givinostat was administered at doses of 10, 30, and 90 mg/kg/day. Treatment-related effects were mainly observed at 90 mg/kg/day and, to a lower extent, at 30 mg/kg/day. Based on overall evaluations, the dose of 10 mg/kg/day was considered the NOAEL in this study.
In general, consistent findings were observed in the oral toxicity studies conducted in the rat. Main changes attributable to the pharmacological action of Givinostat were decreases in peripheral leucocyte numbers (apparent in all leucocyte cell types) and morphological and histopathological changes in lymphoid organs (bone marrow, spleen, lymph nodes). Effects were dose-related, with increased severity observed at the highest tested doses. Reduced platelet number, associated with slightly increased prothrombin time, were also observed in animals treated at the high doses, possibly related to the effects observed in the bone marrow.

In a 4-week oral toxicity study in the Beagle dog, administration of Givinostat once daily for 4 weeks induced treatment-related adverse changes in clinical observations, body weight, food consumption, hematology, blood chemistry, organ weights and microscopic pathology in animals treated at 50 mg/kg/day, and, to a lesser degree, those treated at 25 mg/kg/day. At 12.5 mg/kg/day, the only recorded finding was a slightly higher incidence of loose feces, therefore 12.5 mg/kg/day was considered as NOAEL for Givinostat in this study.

Repeated-dose toxicity studies of different duration (4-, 13- and 39-week) were conducted in the Cynomolgus monkey. In the 4-week oral toxicity study, administration of Givinostat at the high dose (90 mg/kg/day) resulted in toxicity findings (vomiting, hunched posture, piloerection, underactivity, and salivation) which led to discontinuation of treatment after 8 days. The dose was therefore reduced to 60 mg/kg/day, without significant improvement of toxicity signs and treatment was interrupted after 9 days. In this study, Givinostat was in general well tolerated at 10 and 30 mg/kg/day, though a clear no effect level was not identified. Higher doses were considered to exceed the MTD. Based on these findings, in the 13-week oral toxicity study Givinostat was administered at the doses of 3, 10 and 30 mg/kg/day. In this study, treatment-related changes were observed mainly in animals receiving 30 mg/kg/day and the dose of 10 mg/kg/day was identified as the NOAEL. Findings observed in the 39-week study, where Givinostat was administered at the doses of 5, 12 and 30 mg/kg/day, were similar to those observed in the 13-week study and the dose of 12 mg/kg/day was considered the NOAEL in this study. Overall, consistent findings were observed in the oral toxicity studies conducted in the monkey. Effects on RBC and total bilirubin, changes in thymus weight and microscopic changes in liver and thymus were qualitatively similar when comparing the 13- and the 39-week oral toxicity studies performed in this species and were mostly confined to animals given the high doses. The observed treatment-related changes in the red and white blood cell parameters seen in the studies were in general relatively minor in degree, considered of limited or doubtful toxicological significance. There was also no clear indication at histopathological examination

that the disturbances in the blood cell parameters were due to effects on the bone marrow, where only minimal changes (mainly reduced cellularity) were observed. The effects on the WBC observed during the 13- and the 39-week studies can also be associated with the observed lower thymus weights and thymic atrophy/involution, though an add-on stress related effect cannot be excluded.
The liver was identified as a target organ. Increase in hepatic biochemistry parameters (liver enzymes activities, higher bilirubin, urea and triglycerides values) were observed in animals given the highest doses in the studies and were associated with the histopathological finding of bile duct hyperplasia. Liver changes were of limited severity and showed a trend to recovery observed at the end of the recovery period. They were possibly representing a local reaction to the liver metabolic workload and to the likely high concentration of drug-related material in the biliary system in the non-human primate.

Relevance to human usage: None. The relevance of the bile duct hyperplasia finding for patients receiving Givinostat is likely low. This clinical picture is not considered a safety concern.

- reproductive/developmental toxicity
  Reproductive and developmental toxicity studies have been carried out for Givinostat in relevant animal species to evaluate any effects on fertility, embryo-foetal and pre-and post-natal development. Givinostat was administered once daily, by oral gavage. The effect of Givinostat (40, 80, and 160 mg/kg/day) on fertility and early embryonic development was evaluated in male and female Sprague Dawley rats. Treatment was in general well tolerated. All animals mated within 4 days of pairing, with few exceptions at 80 and 160 mg/kg/day, and no differences were found in the number of animals conceiving or siring pregnancy. Compared to control animals, slight changes in uterine parameters were observed on day 14 of gestation (GD14) at 80 and 160 mg/kg/day (higher *corpora lutea* counts, marginally greater number of implantations, higher levels of pre- and post-implantation losses). In males, accessory sex organs were reduced in size at 160 mg/kg/day and to a lesser degree at 80 mg/kg/day. However, no changes were observed in sperm parameters and fertility was not affected. Therefore, the NOAEL for fertility and early embryonic development in the rat was 40 mg/kg/day, both in male and female animals.
  In the embryo-foetal development toxicity study in the Sprague Dawley rat, Givinostat was administered to pregnant females from GD6 to GD17 (corresponding to organogenesis phase in this species) at doses of 40, 80, and 160 mg/kg/day. Fetal examination did not reveal major abnormalities. At 160 mg/kg/day, an increase in incidence of fetuses with structural alterations was observed (thoracic vertebral abnormalities, cervical ribs, 13/14 or 14/14 ribs with associated 20 thoraco-lumbar vertebrae and offset alignment of pelvic girdle). In addition, some minor visceral and skeletal abnormalities were noted (incomplete ossification and increased incidence of partially undescended thymus). Minor findings were also seen at 80 mg/kg/day, though in the absence of an effect on fetal weight the observed findings were not considered to represent an adverse effect of treatment. Therefore, the dose of 80 mg/kg/day is considered the NOAEL for maternal and embryo-fetal development.
  An embryo-foetal development toxicity study was also conducted in the New Zealand White rabbit. Givinostat was administered to pregnant females from GD6 to GD19 (corresponding to organogenesis phase in this species) at doses of 40, 80, and 160 mg/kg/day. The high dose was considered to exceed the MTD for repeated administration to pregnant rabbits. Although at 160 mg/kg/day there was a limited number of litters available for examination, no clear evidence of

embryo-fetal toxicity was observed. At 40 or 80 mg/kg/day there were no treatment-related adverse findings, therefore, the NOAEL for maternal and embryo-fetal toxicity within the context of this study was 80 mg/kg/day.
A pre-and post-natal development toxicity study was conducted in the Sprague Dawley rat. Givinostat was administered to mated females (F0 generation) from GD6 to post-natal day 20 (PND20) at doses of 40, 80, and 160 mg/kg/day. There was no evidence of an adverse effect of maternal treatment on the age of sexual maturation and on the mating performance and fertility of F1 offspring. Therefore, the dose of 80 mg/kg/day was considered the NOAEL for pre- and post-natal development in this study.
Effects of limited to moderate relevance were observed on reproduction and developmental studies after administration of Givinostat in the rat and rabbit.

Relevance to human usage: None.

- genotoxicity
  Givinostat has been examined in several *in vitr*o and *in vivo* genotoxicity assays. In addition, the mutagenic potential was assessed *in vivo* in the mutagenicity assay in a transgenic rodent model.
  In the bacterial reverse mutation assay (Ames test), Givinostat tested positive in two *Salmonella typhimurium* strains screening for frameshift mutations (TA98 and TA1537), in the presence and absence of metabolic activation, but was negative in strains screening for base pair substitutions (TA100, TA102 and TA1535). Givinostat did not induce chromosomal aberrations or increase in polyploid cells in human lymphocytes cultured *in vitro*, and no substantive increases in mutant frequencies were observed in the mutation assay in mouse lymphoma L5178Y cells cultured *in vitro*.
  Givinostat tested negative in the *in vivo* rat bone marrow micronucleus test and in the rat unscheduled DNA synthesis (UDS) test in hepatocytes, following oral treatment at doses up to 2000 mg/kg.
  Mutagenic potential of Givinostat was also evaluated *in vivo* using the Big Blue transgenic rat mutation assay with an additional *Pig-a* mutation analysis, at the doses of 30, 90, and 180 mg/kg/day for 28 consecutive days. Givinostat was negative for the induction of *Pig-a* mutations in mature red blood cells and immature reticulocytes. In the main mutagenicity assay, Givinostat did not induce any statistically significant increase in mutant frequency (MF) at the *cII* gene in liver at all tested doses, and in glandular stomach at the intermediate and low doses. A statistically significant increase in the *cII* MF in glandular stomach was observed at the high dose of 180 mg/kg/day.

  Relevance to human usage: The MF values measured in the control group in this study were relatively low compared to the historical control data and all individual MF values for Givinostat - treated animals were within 95% control limit of the historical vehicle control values. Therefore, the result observed for glandular stomach at the high dose appears to be within the limits of the normal assay variation and could be considered to have little or no biological relevance/significance.

- juvenile toxicity studies
  Two repeated-dose toxicity studies (4- and 13-weeks) were conducted in the juvenile Sprague Dawley rat. A 4-week study was carried out with administration starting at the age of weaning

(25 days of age) to determine systemic toxicity of Givinostat and to examine potential effects on development and fertility.
Givinostat at doses of 20, 60, and 180 mg/kg/day was in general well tolerated. Mating performance and fertility were not affected. The identified NOAEL in this study was 60 mg/kg/day. The toxicological findings observed in the above juvenile study are comparable to that observed in repeated-dose studies in the adult rat. The same pattern of changes was identified in the different parameters evaluated, with the bone marrow identified as a target organ.
A second oral toxicity study was carried out starting at PND7 and lasting up to 14 weeks of age, to assess potential toxicity of Givinostat over a longer period of time. For each treatment group a titration schedule was used by progressively increasing the dose with the animals age (low dose: 10/15/15 mg/kg/day; intermediate dose: 20/30/45 mg/kg/day; high dose: 40/60/90 mg/kg/day), to avoid excessive or insufficient exposure. Givinostat was well tolerated at all tested doses. Results achieved in the juvenile toxicity studies were in line with those observed in other studies in the rat, and no specific concerns are raised for the intended clinical population.

Relevance to human usage: None.

Safety pharmacology

The safety pharmacology profile of Givinostat was studied *in vitro* and *in vivo,* evaluating potential effects on central nervous system (CNS), respiratory, cardiovascular, and gastrointestinal (GI) systems (Table 2).

Table 2. Summary of Givinostat Safety Pharmacology Studies

Study type	Species/ Cell	Route	Dose/Concentrations	Outcome
CNS / Irwin test	CD-1 Mouse	Oral	1, 10, 100 mg/kg	NOEL >100 mg/kg
Cardiovascular system / hERG channel	CHO-K1 cells	NA	0.1, 0.3, 1, 3, 10 µM	IC_{50}= 1.4 µM
Cardiovascular system / Purkinje fibers	Rabbit cardiac fibers	NA	0.1, 0.3, 1, 3, 10 µM	No effects on action potential parameters. At 3 and 10 µM APD_{50} and APD_{90} during bradycardia increased but not statistically significant.
Cardiovascular and respiratory system	Beagle Dog	I.V.	0.1, 1, 10 mg/kg	NOEL ≥10 mg/kg
GI system/ Intestinal charcoal propulsion	CD-1 Mouse	Oral	1, 10, 100 mg/kg	NOEL >100 mg/kg

APD_{50} / APD_{90} = Action Potential Duration at 50% and 90% repolarization; CHO = Chinese Hamster Ovary; hERG = human ether-a-go-go gene; I.V. = intravenous; NA = not applicable; NOEL = No observed effect level.

The potential effect on the cardiovascular system was investigated in *in vitro* and *in vivo* studies. In the hERG assay, Givinostat inhibited hERG K^+ currents with an IC_{50} value of 1.4 µM. The effect of the main metabolites (ITF2374, ITF2375, ITF2440 and ITF2563) of Givinostat was also studied. ITF2374 induced a concentration-dependent inhibition of hERG K^+ tail current with an IC_{50} of 5.7 µM while ITF2375 showed an IC_{50} of 142 µM. ITF2440 and ITF2563 did not show activity on the hERG current at concentrations up to 10^{-4} M. Inhibition of the hERG current is linked to QT interval prolongation, that might result in severe ventricular arrhythmia (Torsade de Pointes). However, the relevance of the *in vitro* data depends on other factors, such as the plasma concentrations reached *in vivo*. A 30-fold margin between free plasma concentrations achieved during clinical use and hERG IC_{50} values can be considered as an adequate threshold to discriminate drugs associated with arrhythmogenic potential. For Givinostat, the maximum plasma levels measured in pediatric and adult subjects receiving the highest doses in clinical studies were generally below 100-150 ng/mL (approximately 200-300 nM). Since about 95% of Givinostat is protein bound, a free C_{max} of about 5 to 7.5 ng/mL (0.01 - 0.015 µM) will be available. Under these conditions, the IC_{50}/free C_{max} ratio is >90 (1.4 µM/0.015 µM), which is well above the indicated 30-fold margin.
The ratios of the free maximum concentrations of the two metabolites ITF2374 and ITF2375 with respect to their IC_{50} values are >1,000 and >10,000-fold, respectively; ITF2440 and ITF2563 did not show activity on hERG current, therefore there appear no concerns for any cardiovascular risk with the considered metabolites.
In addition, no treatment-related effects on ECG parameters and no differences considered to be treatment-related were identified during repeated-dose oral toxicity studies in the dog (4-week oral toxicity study) and in the monkey (13- and 39-week oral toxicity study).

There is no potential risk of phototoxic reactions after administration of ITF2357 since

1) The compound is photostable,
2) No absorption in the visible wavelength range (290-700nm) was seen for ITF2357 and the two main metabolites ITF2374 and ITF2375,
3) Lack of phototoxicity of chemically related compounds (e.g., vorinostat),
4) Clinical and non-clinical findings indicative of phototoxicity were never found after treatment by ITF2357.

Other toxicity-related information or data

No findings in the non-clinical testing warrant inclusion among the summary of safety concerns. However, no carcinogenicity studies are available. According to the ICH guideline, carcinogenicity studies should be performed for any pharmaceutical whose expected clinical use is continuous for at least 6 months or may be expected to be used repeatedly in an intermittent manner. This latter use is consistent with the proposed indications. In addition, the product may be used in the paediatric population. However, for other histone deacetylase inhibitors (e.g., vorinostat), no carcinogenicity studied have been performed. This is in line with the primary pharmacodynamics of this therapeutic class. HDAC inhibitors induce cancer cell cycle arrest, differentiation, and cell death, reduce angiogenesis and modulate immune response. In conclusion, the current absence of carcinogenicity studies for ITF2357 cannot be considered as a missing information and is not expected to be carried

forward to sections SVII and SVIII as a risk. Two-year carcinogenicity studies in two rodent species (mouse and rat) have been planned to evaluate the carcinogenic potential of Givinostat.

Relevance to human usage: The exposure-based safety margin ratios for Givinostat were calculated comparing the systemic exposure data obtained in the rat and the monkey at the respective NOAELs in the chronic studies (10 and 12 mg/kg/day, respectively) and the exposure values obtained in DMD patients after 1 year of treatment at the representative doses of 25 and 37.5 mg b.i.d.

The calculated exposure-based safety margins were lower than 1 for the rat considering both human doses, while for the monkey safety margins are greater than 1 when considering the 25 mg dose, while for the higher dose of 37.5 mg a margin higher than 1 is only obtained for C_{max} values. The low values at the NOAELs are likely related to the greater biotransformation and/or to the shorter half-life of Givinostat occurring in the nonclinical species compared to humans.

In addition, different dose-limiting toxicities observed comparing nonclinical species and humans can account for these differences. All the effects observed in nonclinical studies at doses above the NOAEL were indicative of treatment-related inhibition of the bone marrow functionality, resulting in hematological changes. This was monitored in the clinical setting, and dose-limiting effects observed in DMD patients were also consistent with imbalance in bone marrow functionality.

In humans, a different sensitivity in the cell lineage was identified, being the decrease in peripheral platelets count the most sensitive endpoint. Gastrointestinal intolerance was also identified as a main side effect in human subjects receiving Givinostat. This finding was occasionally observed in the representative nonclinical species.

Therefore, this partial lack of safety margin over human therapeutic exposure is not considered a safety concern for the clinical use of Givinostat, being the qualitative toxicological profile similar across species (same target organ toxicity), the target organ toxicity considered consequent to the pharmacology of Givinostat and occurring at high doses. The effect is effectively monitorable in the nonclinical studies and in the clinical setting and the clinical experience accumulated so far is indicative of reversibility of the effects after treatment withdrawal.

No safety concern originating from pre-clinical studies is considered important for inclusion in Part II, Module SVIII.

Part II: Module SIII - Clinical trial exposure

SIII.1. Brief Overview of Development

Duchenne Muscular Dystrophy Patients

The applicant carried out three clinical trials that enrolled 222 DMD patients (treated with standard therapy + givinostat) and, among them, 61 patients treated with standard therapy + placebo. The drug has been tested in a pilot phase II study and a phase III double blind, placebo-controlled study. An open-label long term safety and efficacy study is also ongoing. The most common dose category of givinostat was between 13.3 to 46.7 mg b.i.d., based on patients' weight (40.9%). The median treatment duration of givinostat in the DMD studies was 24.9 months (range 0.6 to 105 months).

Table SIII.1: Duration of exposure

	Givinostat (DUVYZAT)					**Placebo**
	A N=32	**B N=91**	**A-B-C N=69**	**B-C N=30**	**Givinostat Overall N=222**	**Overall N=61**
Number of weeks in the studies						
Mean (SD)	158.13 (111.44)	84.65 (36.41)	217.73 (128.64)	78.85 (35.61)	135.82 (105.95)	80.87 (10.12)
Median	140.43	79.00	194.29	76.50	108.29	78.86
Min; Max	9.1; 454.3	2.4; 146.3	25.3; 456.6	17.3; 146.7	2.4; 456.6	39.0; 121.3
Number of months in the studies						
Mean (SD)	36.37 (25.63)	19.47 (8.37)	50.07 (29.58)	18.13 (8.19)	31.24 (24.37)	18.60 (2.33)
Median	32.30	18.17	44.68	17.59	24.90	18.14
Min; Max	2.1; 104.5	0.6; 33.6	5.8; 105.0	4.0; 33.7	0.6; 105.0	9.0; 27.9

Dose level A: ranging from 20 to 70 mg b.i.d, based on patients' weight; dose level B: ranging from 13.3 to 46.7 mg b.i.d., based on patients' weight; dose level C: ranging from 10.6 to 37.4 mg b.id., based on patients' weight.

Table SIII.2: Age group gender and ethnic origin

	Givinostat (DUVYZAT)					Placebo
	A N=32	**B N=91**	**A-B-C N=69**	**B-C N=30**	**Givinostat Overall N=222**	**Overall N=61**
Age (years)						
n	32	91	69	30	222	61
Mean (SD)	9.6 (1.9)	10.4 (2.4)	9.9 (2.1)	10.3 (1.9)	10.1 (2.2)	10.0 (2.1)
Median	9.9	10.3	9.9	10.1	10.0	9.9
IQ Range	7.8; 10.9	8.7; 12.2	8.0; 11.4	8.9; 11.9	8.3; 11.5	8.3; 11.4
Min ; Max	7; 15	6; 16	6; 15	7; 14	6; 16	6; 14
Age categories (years)						
6 to <12	29 (90.6)	66 (72.5)	54 (78.3)	23 (76.7)	172 (77.5)	49 (80.3)
≥12 to < 18	3 (9.4)	25 (27.5)	15 (21.7)	7 (23.3)	50 (22.5)	12 (19.7)
Sex (n (%))						
Male	32 (100.0)	91 (100.0)	69 (100.0)	30 (100.0)	222 (100.0)	61 (100.0)
Race (n (%))						
Asian	3 (9.4)	3 (3.3)	2 (2.9)	0	8 (3.6)	2 (3.3)
Black/African American	0	3 (3.3)	0	1 (3.3)	4 (1.8)	0
White	28 (87.5)	78 (85.7)	64 (92.8)	28 (93.3)	198 (89.2)	57 (93.4)
Other	1 (3.1)	7 (7.7)	3 (4.3)	1 (3.3)	12 (5.4)	2 (3.3)
Not Reported	0	0	0	0	0	0

Table SIII.3: Dose

	Givinostat (DUVYZAT)					Placebo
	A N=32	**B N=91**	**A-B-C N=69**	**B-C N=30**	**Givinostat Overall N=222**	**Overall N=61**
Number of patients included in the safety set (n (%))	32 (100.0)	91 (100.0)	69 (100.0)	30 (100.0)	222 (100.0)	61 (100.0)

Dose level A: ranging from 20 to 70 mg b.i.d, based on patients' weight; dose level B: ranging from 13.3 to 46.7 mg b.i.d., based on patients' weight; dose level C: ranging from 10.6 to 37.4 mg b.id., based on patients' weight.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Platelets count at screening < Lower Limit of Normal

Reason for exclusion: To maximise the safety of treated patients.

Is it considered to be included as missing information? No

Rationale: Dose-related platelet count reduction is an important identified risk of Givinostat (risk of haemorrhage).

Symptomatic cardiomyopathy or heart failure (New York Heart Association Class III or IV) or left ventricular ejection fraction <50%

Reason for exclusion: To maximise the safety of treated patients.

Is it considered to be included as missing information? No

Rationale: Standard exclusion criterium.

Liver disease or impairment

Reason for exclusion: To maximise the safety of treated patients.

Is it considered to be included as missing information? Yes

Rationale: Standard exclusion criterium.

Inadequate renal function, as defined by serum Cystatin C >2 x the upper limit of normal

Reason for exclusion: To maximise the safety of treated patients.

Is it considered to be included as missing information? Yes

Rationale: Standard exclusion criterium.

Baseline QTcF >450 msec, (as the mean of 3 consecutive readings 5 minutes apart) or history of additional risk factors for torsades de pointes (e.g., heart failure, hypokalaemia, or family history of long QT syndrome)

Reason for exclusion: To maximise the safety of treated patients.

Is it considered to be included as missing information? No

Rationale: Standard exclusion criteria.

Reason for exclusion: Treated patients are only males.

Is it considered to be included as missing information? No

Rationale: Age and gender of DMD patients.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	**Exposure**
Pregnant women	Not included in the clinical development program, but not representative of the target population
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment (serum Cystatin C >2 x the upper limit of normal) • Patients with cardiovascular impairment (Symptomatic cardiomyopathy or heart failure (New York Heart Association Class III or IV) or left ventricular ejection fraction <50%; Baseline QTcF >450 msec, (as the mean of 3 consecutive readings 5 minutes apart) or history of additional risk factors for torsades de pointes (e.g., heart failure, hypokalaemia, or family history of long QT syndrome) • Immunocompromised patients (HIV patients) • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Only a non-significant number of subjects were of non-Caucasian origin.
Subpopulations carrying relevant genetic polymorphisms	Not applicable.
Other	Not applicable.

Part II: Module SV - Post-authorisation experience

Not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Givinostat has no potential for misuse for illegal purposes, e.g., as a recreational drug or to facilitate assault. Therefore, no means of limiting this are included in the risk minimisation plan.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Non-specific gastrointestinal symptoms, including vomiting and diarrhoea (managed by dose adjustments).

- Non-specific, mild infections, including those typical of the paediatric age

- Pyrexia

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

Leukopenia.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised):

Not applicable.

Known risks that do not impact the risk-benefit profile

None

Other reasons for considering the risks not important:

None

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risks: None

Important Potential Risk 1: Haemorrhagic disorders

Risk-benefit impact: Although thrombocytopenia has not been associated with serious bleeding events, the risk of haemorrhagic disorders in overdose is a potential safety concern.

Important Potential Risk 2: Clinical consequences of hypertriglyceridaemia (e.g., pancreatitis, coronary artery disease, hepatic steatosis)

Risk-benefit impact: Although hypertriglyceridemia has several clinical consequences such as pancreatitis, coronary artery disease and hepatic steatosis, these were not observed in clinical studies with givinostat.

Important Potential Risk 3: Dehydration with potential electrolyte imbalance

Risk-benefit impact: Diarrhoea is the most frequent adverse event seen during therapy with Givinostat in clinical trials, accounting for 38.7% of treated patients. Consequently, a potential risk of dehydration has been considered, considering that the target population is mostly of paediatric age. Possible electrolyte imbalance (e.g., hypokalaemia) due to dehydration may also trigger ECG abnormalities (*see QTc interval prolongation*).

Missing information: **Long-term safety (no MedDRA code available)**

Risk-benefit impact: The treatment of DMD with givinostat is considered to be chronic treatment starting at a young age. Currently, the safety database of the applicant encompasses a total of 222 patients treated with givinostat with a median duration of exposure of 24.9 months. Therefore, long-term safety of givinostat is considered as a missing information.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Potential Risk 1: Haemorrhagic disorders (10019009); Haemorrhage (10055798)

Potential mechanisms: Thrombocytopenia may potentially cause bleedings of clinical significance.

Evidence source(s) and strength of evidence: A decrease in platelet count has been observed in more than 10% of DMD patients treated with givinostat. However, no major bleedings have been recorded in clinical studies.

Characterisation of the risk: This risk is included as potential, being the clinical correlate of a laboratory finding.

Risk factors and risk groups: A correlation between body weight (and dose) with platelet decrease has been observed. Therefore, heavier patients could be exposed to a higher risk if dose is not adjusted.

Preventability: Regular monitoring of platelet counts, and possible dose decrease or interruption of givinostat.

Impact on the risk-benefit balance of the product: Platelets' counts are managed by dose changes, without further interventions.

Public health impact: Although no haemorrhagic episode has been recorded during clinical studies with givinostat, the public health impact of this risk is not assessable at the time of this version of the RMP.

Important Potential Risk 2: Clinical consequences of hypertriglyceridaemia (e.g., pancreatitis, coronary artery disease, hepatic steatosis)
(Pancreatitis- 10033645; Coronary artery disease – 10011078; Hepatic steatosis - 10019708)

Potential mechanisms: Hypertriglyceridemia is one of the major causes of acute pancreatitis, coronary artery disease, and hepatic steatosis.

Evidence source(s) and strength of evidence: An increase in blood triglycerides has been observed in more than 10% of DMD patients treated with givinostat. Clinical consequences have not been observed.

Characterisation of the risk: Hypertriglyceridemia has been identified as a risk factor for acute pancreatitis, coronary artery disease, and hepatic steatosis – even when plasma levels are only mildly elevated.

Risk factors and risk groups: Serum triglyceride levels > 1000 mg/dl are thought to be necessary to induce pancreatitis, however, there is no clear threshold above which hypertriglyceridemia is known to trigger acute pancreatitis. In addition, hypertriglyceridemia may be an important contributor of the residual risk of cardiovascular disorders [**Sandesara PB, 2019**]. Metabolic (dysfunction) associated fatty liver disease (MAFLD) is linked to hypertriglyceridemia and is also associated with an increased cardiovascular disease risk [**Badmus OO, 2022**].

Preventability: Regular monitoring of triglycerides and possible dose decrease or interruption.

Impact on the risk-benefit balance of the product: Hypertriglyceridemia is managed by dose adjustments, without further interventions.

Public health impact: Although no pancreatitis, coronary heart disease and hepatic steatosis has been recorded during clinical studies with givinostat, the public health impact of this risk is not assessable at the time of this version of the RMP.

Important Potential Risk 3: Dehydration with potential electrolyte imbalance (Dehydration – 10012174; Electrolyte imbalance - 10014418)

Potential mechanisms: Dehydration with potential electrolyte imbalance may originate from diarrhoea, especially if persistent or severe (grade 3-4 according to the Common Terminology Criteria for Adverse Events [CTCAE], version 5.0 of the U.S. Department of Health and Human Services).

Evidence source(s) and strength of evidence: Diarrhoea is the most frequent adverse event seen during therapy with Givinostat in clinical trials, accounting for 38.7% of treated patients vs. 18% of subjects taking placebo. Consequently, a potential risk of dehydration has been considered.

Characterisation of the risk: Diarrhoea may cause dehydration and subsequently to electrolyte disturbances (e.g., hypokalaemia) associated with cardiovascular events (tachycardia, ECG abnormalities and hypotension), confusion, dizziness, gastrointestinal disturbances, and a constellation of non-specific symptoms.

Risk factors and risk groups: Not identified.

Preventability: Possible dose decrease or interruption.

Impact on the risk-benefit balance of the product: At the time of this version of the RMP, diarrhoea has been observed as an isolated event, not associated with clinical signs of dehydration in patients treated with givinostat.

Public health impact: Not identified.

SVII.3.2. Presentation of the missing information

Missing information 1: Long-term safety (no MedDRA code available)

Evidence source: The treatment DMD with Givinostat is considered to be chronic treatment starting at a young age. Currently, the safety database of the applicant encompasses a total of 222 patients treated with Givinostat at four different dose levels, with a median duration of exposure of 24.9 months. Therefore, long-term safety of givinostat is considered as missing information.

Population in need of further characterisation: An open label, long-term safety, tolerability, and efficacy study to assess the safety and tolerability of long-term administration of givinostat is currently ongoing (DSC 11/2357/51; EUDRACT no.: 2017-000397-10).

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Haemorrhagic disorders Clinical consequences of hypertriglyceridaemia (e.g., pancreatitis, coronary artery disease, hepatic steatosis) Dehydration with potential electrolyte imbalance
Missing information	Long-term safety

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

None.

III.2 Additional pharmacovigilance activities

Observational PAES study, please refer to Part IV and Annex V

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable

Part IV: Plans for post-authorisation efficacy studies

Study Title and Status	Summary of objectives	Efficacy and Safety concerns addressed	Milestones	Due dates
Efficacy study that is a specific obligation in the context of a conditional marketing authorisation or a marketing authorization under exceptional circumstances				
Title: A prospective, observational, long-term, multinational, post-authorization study in ambulant patients 6 years and older with DMD treated with Givinostat oral suspension (DUVYZAT) and with concomitant corticosteroid treatment. **Status:** planned	To investigate the long-term safety profile and the long-term effectiveness of givinostat within the target age group under conditions of routine clinical care, based on data from sites and/or patient registries	Primary endpoint: • Long term effectiveness Secondary endpoints: • Clinical consequences of hypertriglyceridaemia (e.g., pancreatitis, coronary artery disease, hepatic steatosis) • Haemorrhagic disorders, including severe bleeding • Dehydration with potential electrolyte imbalance • Long-term safety	Protocol submission Interim report Final report	June 2026 December 2029 / December 2031 / December 2033 / December 2035 December 2037

Study Name and Status	Summary of objectives	Efficacy and Safety concerns addressed	Milestones	Due dates
Efficacy study that is a specific obligation in the context of a conditional marketing authorisation or a marketing authorization under exceptional circumstances				
Randomised, double blind, placebo controlled, multicentre	To provide further evidence of efficacy and safety of	Efficacy and safety	Protocol submission	June 2026

study to provide further data regarding the efficacy and safety of givinostat in ambulant patients with Duchenne Muscular Dystrophy in combination with the EPIDYS study results (Meta-RCT) **Status:** Planned	givinostat in ambulant DMD subjects		Final report	31 July 2033

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern.

Safety concern	**Routine risk minimisation activities**
Haemorrhagic disorders (*potential*)	Routine risk communication: *SmPC sections 4.2, and 4.4* *PL sections 2 and 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: ***Recommendations for platelet count monitoring and need for dosing interruption and/or treatment discontinuation are included in SmPC sections 4.2 and 4.4*** Other routine risk minimisation measures beyond the Product Information: Legal status: Product on restricted medical prescription

Clinical consequences of hypertriglyceridaemia (e.g., pancreatitis, coronary artery disease, hepatic steatosis)	Routine risk communication:

(*potential*)	*SmPC sections 4.2, and 4.4* *PL sections 2 and 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: ***Recommendations for triglycerides monitoring and need for dosing interruption and/or treatment discontinuation are included in SmPC sections 4.2 and 4.4.*** Other routine risk minimisation measures beyond the Product Information: Legal status: Product on restricted medical prescription

Safety concern	**Routine risk minimisation activities**
Dehydration with potential electrolyte imbalance (*potential*)	Routine risk communication: *SmPC sections 4.2, and 4.4 PL sections 2 and 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: ***Recommendations on the need for dosing interruption and/or treatment discontinuation in case of moderate or severe diarrhoea are included in SmPC sections 4.2 and 4.4*** Other routine risk minimisation measures beyond the Product Information: Legal status: Product on restricted medical prescription

Safety concern	**Routine risk minimisation activities**
Long-term safety (*missing information*)	Routine risk communication: *None* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: Legal status: Product on restricted medical prescription

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Haemorrhagic disorders (*potential*)	Routine risk minimisation measures: *SmPC sections 4.2 and 4.4 where advice is given on dose adjustment and monitoring blood platelet counts* *PL sections 2 and 4* Additional risk minimisation measures: no risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: observational PAES study
Clinical consequences of hypertriglyceridaemia (e.g., pancreatitis, coronary artery disease, hepatic steatosis) (*potential*)	Routine risk minimisation measures: *SmPC sections 4.2 and 4.4 where advice is given on dose interruption and adjustment and monitoring blood triglycerides* *PL sections 2 and 4* Additional risk minimisation measures: no risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: observational PAES study
Dehydration with potential electrolyte imbalance (*potential*)	Routine risk minimisation measures: *SmPC sections 4.2 and 4.4 where advice is given on dose adjustment in case of severe diarrhoea* *PL sections 2 and 4* Additional risk minimisation measures: no risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: observational PAES study

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long-term safety (*missing information*)	Routine risk minimisation measures: Additional risk minimisation measures: no risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: observational PAES study

Part VI: Summary of risk management plan

This is a summary of the risk management plan (RMP) for DUVYZAT oral suspension. The RMP details important risks of DUVYZAT, how these risks can be minimised, and how more information will be obtained about DUVYZAT 's risks and uncertainties (missing information).

DUVYZAT 's summary of product characteristics (SmPC) and its package leaflet will give essential information to healthcare professionals and patients on how DUVYZAT should be used.

This summary of the RMP for DUVYZAT should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of DUVYZAT 's RMP.

I. The medicine and what it is used for

DUVYZAT is indicated for the treatment of Duchenne muscular dystrophy (DMD) in ambulant patients, aged 6 years and older, and with concomitant corticosteroid treatment.

It contains Givinostat HCl as the active substance and it is given by an 8.86mg/mL oral suspension.

Further information about the evaluation of DUVYZAT's benefits can be found in DUVYZAT's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of DUVYZAT, together with measures to minimise such risks and the proposed studies for learning more about DUVYZAT 's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of DUVYZAT is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of DUVYZAT are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of DUVYZAT. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Summary of safety concerns	
Important identified risks	None
Important potential risks	Haemorrhagic disorders Clinical consequences of hypertriglyceridaemia (e.g., pancreatitis, coronary artery disease, hepatic steatosis) Dehydration with potential electrolyte imbalance
Missing information	Long-term safety

II.B Summary of important risks

Important potential risk: Haemorrhagic disorders	
Evidence for linking the risk to the medicine	Dose-related platelet count decreased, and thrombocytopenia (i.e. clinically significant platelet abnormalities) were reported in 23% and 18% of patients on givinostat, respectively.
Risk factors and risk groups	Not identified.
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.2, and 4.4* *SmPC sections 4.2 and 4.4 where advice is given on dose adjustment and monitoring blood platelet counts* Do not initiate givinostat in patients with a platelet count less than 150 x 10^9/L. *PL sections 2 and 4* Additional risk minimisation measures No risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: observational PAES study.

Important potential risk: Clinical consequences of hypertriglyceridaemia (e.g., pancreatitis, coronary artery disease, hepatic steatosis)	
Evidence for linking the risk to the medicine	Blood triglycerides increased/ hypertriglyceridaemia were more frequently reported with givinostat compared to placebo (25.2% vs. 6.6%).
Risk factors and risk groups	In patients with underlying dyslipidaemia, a secondary cause of hypertriglyceridemia may result in clinically significant increases in triglyceride levels that could lead to acute pancreatitis, cardiovascular disorders and hepatic steatosis.
Risk minimisation measures	Routine risk minimisation measures:

	SmPC sections 4.2, and 4.4 *SmPC sections 4.2 and 4.4 where advice is given on dose interruption and adjustment and monitoring blood triglycerides* Triglycerides levels should be measured before starting. *PL sections 2 and 4* Additional risk minimisation measures No risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: observational PAES study.

Important potential risk: Dehydration with potential electrolyte imbalance	
Evidence for linking the risk to the medicine	Diarrhoea is the most frequent adverse event seen during therapy with Givinostat in clinical trials, accounting for 38.7% of treated patients vs. 18% of subjects taking placebo. Consequently, a potential risk of dehydration has been considered.
Risk factors and risk groups	Not identified.
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.2, and 4.4* *SmPC sections 4.2 and 4.4 where advice is given on dose adjustment in case of severe diarrhoea* *PL sections 2 and 4* Additional risk minimisation measures No risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: observational PAES study.
Missing information: Long-term safety	
Evidence for linking the risk to the medicine	The treatment of DMD with givinostat is considered to be chronic treatment, starting at a young age. Currently, the safety database of the applicant encompasses 222 patients treated with givinostat at four different dose levels, with a median duration of exposure of 24.9 months.
Risk minimisation measures	Routine risk minimisation measures:

	Additional risk minimisation measures No risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: observational PAES study.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

Post-authorisation efficacy studies (PAESs)

Title: A prospective, observational, long-term, multinational, post-authorization study in ambulant patients 6 years and older with DMD treated with Givinostat oral suspension (DUVYZAT) and with concomitant corticosteroid treatment.
Purpose: Primary objective: • To investigate the long-term effectiveness of givinostat within the target age group under conditions of routine clinical care. Secondary objective: • To investigate the long-term safety profile of givinostat within the target age group under conditions of routine clinical care.

Title: Randomised, double blind, placebo controlled, multicentre study to provide further data regarding the efficacy and safety of givinostat in ambulant patients with Duchenne Muscular Dystrophy in combination with the EPIDYS study results (Meta-RCT)
Purpose: • To provide further evidence of efficacy and safety of givinostat in ambulant DMD subjects

II.C.2 Other studies in post-authorisation development plan

Not appliable

Part VII: Annexes

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