ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Duvyzat 8.86 mg/ml oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 8.86 mg givinostat (as hydrochloride monohydrate).

Excipient(s) with known effect
Each ml contains 4.4 mg of sodium benzoate (E211).
Each ml contains 400 mg of sorbitol (E420).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension.
White to off-white or faintly pink, homogenous suspension when mixed.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Treatment with givinostat should be initiated by a physician experienced in the management of Duchenne muscular dystrophy.

Posology

Baseline platelet counts and triglycerides should be obtained and evaluated prior to initiation of givinostat. Givinostat should not be initiated in patients with a platelet count less than 150 x 10^9/l. Platelet counts and triglycerides should be monitored as recommended during treatment to determine if dosage modifications are needed (see section 4.4 and dose adjustment instructions below).

In addition, in patients with underlying cardiac disease or taking concomitant medicines that cause QT prolongation, an ECG should be obtained when initiating treatment with givinostat, during concomitant use, and as clinically indicated (see section 4.4).

The recommended dose of givinostat is based on body weight and should be administered orally twice daily (see Table 1).

Table 1 – Recommended Dosage

Weight[a]	Dosage	Oral suspension volume
15 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

[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

	First Dosage Modification[b]		Second Dosage Modification[c]	
Weight[a]	**Dosage**	**Oral Suspension Volume**	**Dosage**	**Oral Suspension Volume**
15 kg to less than 20 kg	17.7 mg twice daily	2 ml twice daily	13.3 mg twice daily	1.5 ml twice daily
20 kg to less than 40 kg	22.2 mg twice daily	2.5 ml twice daily	17.7 mg twice daily	2 ml twice daily
40 kg to less than 60 kg	31 mg twice daily	3.5 ml twice daily	26.6 mg twice daily	3 ml twice daily
60 kg or more	39.9 mg twice daily	4.5 ml twice daily	35.4 mg twice daily	4 ml twice daily

[a] Based on actual body weight
[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.

Patients should not take a double or extra dose if a dose is missed.

Paediatric population
The efficacy and safety of Duvyzat in children below 6 years of age has not been established. No data are available.

Method of administration

For oral use.
Before its use, the suspension must be shaken for at least 30 seconds by rotating the bottle by 180° for approximately 40 times, and the homogeneity of the suspension should be visually verified.
Incorrect shaking may lead to over dosing or under dosing.
Duvyzat must be taken as it is (i.e. not to be diluted in/with water or other liquids).
The suspension should be administered using the provided graduated oral syringe to measure the appropriate volume of suspension corresponding to the prescribed dose for the patient.
Duvyzat should be administered with the ingestion of food to mitigate the bitter taste of givinostat.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Haematological effects

Givinostat is associated with dose-related thrombocytopenia and other signs of myelosuppression, including decreased haemoglobin and neutropenia.
The effect is most prominent in platelet counts (see section 4.8).
A complete blood count should be obtained before starting treatment with givinostat. Platelet counts should be closely monitored during treatment with givinostat, i.e. every 2 weeks for the first 2 months of treatment, at month 3, and then every 3 months thereafter.

In case of persistent thrombocytopenia, the dose of givinostat should be adjusted. Treatment should be discontinued if the abnormalities are still persistent (see section 4.2).
In patients with dose increased due to weight gain, platelet count should be closely monitored every 2 weeks for the first 2 months after the dose was increased.

Increased triglycerides

Givinostat is associated with increased serum triglycerides.
Triglycerides levels should be measured before starting treatment with givinostat.
Triglycerides should be monitored at least on the third month, on the sixth month and then every 6 months.
In DMD patients with persistent increase in triglycerides levels in fasting condition (> 300 mg/dl), the dose of givinostat should be adjusted as indicated in section 4.2.
Treatment with givinostat should be discontinued if triglycerides remain elevated despite adequate dietary intervention and dosage adjustment (see section 4.2).

Gastrointestinal disturbances

Diarrhoea and vomiting were very common adverse drug reactions in givinostat clinical trials in DMD (see section 4.8).
Diarrhoea and vomiting usually occur within the first few weeks of initiation of treatment with givinostat.
Antiemetics or antidiarrhoeal medications may be considered during treatment with givinostat.
Fluid and electrolytes should be replaced as needed to prevent dehydration.

The dose of givinostat should be adjusted in case of moderate or severe diarrhoea (more than 4 stools per day) (see section 4.2).
Treatment should be discontinued if the abnormalities are still persistent (see section 4.2).

QTc prolongation

Givinostat can cause prolongation of the QTc interval at doses 5-fold higher than the recommended dose.
Givinostat should be used with caution in patients who are at an increased risk for ventricular arrhythmias (including torsades de pointes), patients with congenital long QT syndrome, coronary artery disease, electrolyte disturbances, or concomitant use of other medicinal products known to cause QT prolongation. In these patients, ECGs should be obtained when initiating treatment with Duvyzat, during concomitant use, and as clinically indicated.
In patients with hypokalaemia this should be corrected prior to initiation of givinostat and monitored in case of dehydration due to diarrhoea.
Duvyzat should be withheld if the QTc interval is > 500 ms or the change from baseline is > 60 ms.

Excipients with known effects

Patients with hereditary fructose intolerance (HFI) should not take this medicinal product.
This medicinal product contains 400 mg sorbitol in each ml which is equivalent to 40 mg/kg.
The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.
The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

This medicinal product contains 4.4 mg sodium benzoate in each ml which is equivalent to 0.44 mg/kg.
This medicinal product contains less than 1 mmol sodium (23 mg) per dose and therefore, is essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Caution is advised when prescribing Duvyzat with medicinal products known to prolong the QT interval with known or possible risk for torsades de pointes, e.g. anaesthetics (e.g. sevoflurane, propofol), class III antiarrhythmics (e.g. amiodarone, sotalol), antiemetics (ondansetron), antibiotics (azithromycin, clarithromycin, ciprofloxacin), antimycotics (fluconazole), antipsychotics (aripiprazole, risperidone), and antihistamines (e.g. famotidine). This list is indicative and not exhaustive.

The effect of concomitant use of Duvyzat with antithrombotic medications on platelets count is unknown.

Duvyzat should be used with caution in patients taking concomitant medication known to increase triglyceride values as it might increase the risk for hypertriglyceridaemia.

Effect of givinostat on pharmacokinetics of other medicinal products

A weak CYP3A4 inhibition, mainly in the intestine was shown in a Drug-Drug Interaction (DDI) study in humans. Caution should be exercised when givinostat is co-administered with medicinal products that are substrates of CYP3A4 and have a narrow therapeutic margin.

The potential to inhibit the intestinal transporter protein P-gp cannot be excluded. Medicinal products known to be a substrate of the P-gp transporter and have a narrow therapeutic margin should be used with caution with givinostat.

A weak inhibition of the renal uptake transporter OCT2 was seen *in vitro* and in clinical trials with givinostat by creatinine measurements. Medicinal products known to be a substrate of the OCT2 transporter and have a narrow therapeutic margin should be used with caution with givinostat.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of givinostat in pregnant women. Animal studies have shown reproductive toxicity (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of givinostat during pregnancy.

Breast-feeding
It is unknown whether givinostat or its metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. Givinostat should not be used during breast-feeding.

Fertility
There are no human data on the effect of givinostat on fertility. Givinostat showed adverse effects on accessory glands in male rats, however, fertility of animals was not affected (see section 5.3). The relevance for humans is not known.

4.7 Effects on ability to drive and use machines

Givinostat may have a minor influence on the ability to drive and use machines.
Dizziness and fatigue may occur following administration of givinostat (see section 4.8).

4.8 Undesirable effects

Summary of safety profile

The safety profile of Duvyzat is based on a phase 3, double-blind, placebo-controlled, 18-months study in a total of 179 ambulant DMD patients aged 6 years or older on concomitant steroid treatment, of which 118 receiving givinostat up to 62 mg twice daily and 61 receiving placebo (EPIDYS Study).

The most common events occurring in the placebo-controlled study (based on aggregated terms where applicable) were diarrhoea (38.1%), abdominal pain (33.9%), thrombocytopenia (32.2%), vomiting (28.8%) and hypertriglyceridaemia (22.9%).

Tabulated list of adverse reactions

Adverse reactions are listed below according to MedDRA system organ class and frequency (see Table 3). The table contains adverse events reported in givinostat-treated patients at a frequency greater than 2% compared to placebo-treated patients in EPIDYS study.

Frequency groupings are defined to the following convention: Very common (≥1/10) and common (≥1/100 to <1/10) uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); frequency not known (cannot be estimated from the available data).

Table 3 – Adverse Drug Reactions reported in givinostat-treated patients at a frequency greater than 2% compared to placebo-treated patients in the placebo-controlled EPIDYS Study

System Organ Class	Very common	Common
Infections and infestations		Gastroenteritis
Blood and lymphatic system disorders	Thrombocytopenia[(a)]	
Metabolism and nutrition disorders	Hypertriglyceridaemia[(b)]	Decreased appetite
Psychiatric disorders		Anxiety
Nervous system disorders		Dizziness
Vascular disorders		Haematoma
Gastrointestinal disorders	Diarrhoea[(c)], Vomiting, Abdominal pain[(d)]	Constipation
Skin and subcutaneous tissue disorders		Erythema, Rash
Musculoskeletal and connective tissue disorders		Myalgia, Arthralgia, Muscular weakness
General disorders and administration site conditions	Pyrexia	Fatigue
Investigations		Blood thyroid stimulating hormone increased[(e)]

[(a)] Thrombocytopenia includes platelet count decreased and thrombocytopenia;
[(b)] Hypertriglyceridaemia includes hypertriglyceridaemia and blood triglycerides increased;
[(c)] Diarrhoea includes diarrhoea and faeces soft;
[(d)] Abdominal pain includes abdominal pain and abdominal pain upper;
[(e)] Blood thyroid stimulating hormone increased includes thyroid function test abnormal and blood thyroid stimulating hormone increased.

Description of selected adverse reactions

Haematological changes
Givinostat has been shown to reduce platelet count with the greatest reduction observed after approximately 88 days and platelet counts remained low throughout treatment. There were no serious bleeding events related to thrombocytopenia. After givinostat dose reduction, platelets return to normal values in approximately 3-4 weeks.
Thrombocytopenia occurred in 32.2% of patients treated with Duvyzat and in no patient on placebo. Of these reactions, 86.8% were reported as mild and 13.2% as moderate.
Low platelet counts resulted in Givinostat dose reduction in 28% of patients. Patients with baseline platelet counts below the lower limit of normal were excluded from the studies.
Decreased haemoglobin and decreased neutrophils were also observed in patients treated with givinostat compared to placebo.

Triglyceride changes
Givinostat has been shown to increase triglyceride levels, with the greatest increase observed after approximately 221 days. After givinostat dose interruption, triglyceride levels return to baseline values in approximately 90 days.
High triglycerides (i.e., levels > 300 mg/dl) resulted in discontinuation and led to dosage modification in 2% and 8%, respectively, of patients treated with Duvyzat.
Hypertriglyceridaemia occurred in 22.9% of patients treated with Duvyzat. Of these events, 70.4% were reported as mild, 25.9% as moderate and in one case (3.7%) as severe.

Gastrointestinal disturbances
Gastrointestinal disturbances, including diarrhoea, vomiting and abdominal pain occurred in patients treated with givinostat.
Diarrhoea was reported in 38% of patients treated with Duvyzat (with 1 severe case reported) compared to 18% of patients on placebo. Diarrhoea usually occurred within the first few weeks of initiation of treatment with Duvyzat.
Vomiting occurred in 29% of patients treated with Duvyzat (with 2 severe cases reported) compared to 13% of patients on placebo. Vomiting usually occurred within the first 2 months of treatment.
Abdominal pain occurred in 34% of patients treated with Duvyzat compared to 23% of patients on placebo. One case of abdominal pain was serious.

Description of other laboratory abnormalities
Adverse reactions of hypothyroidism and/or thyroid stimulating hormone (TSH) increased occurred in 5% of patients treated with Duvyzat compared to 2% of patients who received placebo.
In addition, hypothyroidism (common) events were observed during long-term treatment.
Blood thyroid stimulating hormone levels were generally within 2 times the upper limit of normal with no or minor changes in thyroid hormones.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In the event of a suspected overdose, supportive medical care, including cardiac monitoring should be provided.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other drugs for disorders of the musculoskeletal system, ATC code: M09AX14.

Mechanism of action

Givinostat is a class I and II histone deacetylase (HDAC) inhibitor that modulates the uncontrolled HDAC activity in dystrophic muscles, which contributes to the pathology of Duchenne muscular dystrophy (DMD).
Givinostat HDAC inhibition has been shown to reduce muscle fiber damage, chronic muscular inflammation, fibrosis, fat deposition, and to promote mitochondrial biogenesis.
Givinostat mechanism of action is independent of the underlying dystrophin gene mutation causing the disease.

Muscle fat fraction as assessed by MR spectroscopy

The percentage of fat fraction present in the vastus lateralis muscles (VLM) of the thigh was measured in EPIDYS Study using magnetic resonance spectroscopy. At 18 months, for the patients with baseline VLM fat fraction in the range of > 5% to ≤ 30%, a LS mean increase of VLM fat fraction was 7.63% in the Duvyzat-treated patients compared to a 10.56% increase in patients who received placebo.

Clinical efficacy and safety

The safety and efficacy of Duvyzat in DMD patients were assessed in EPIDYS study. EPIDYS was a 18 months, 2:1 randomised, double-blind, placebo-controlled phase 3 study of 179 ambulant DMD patients aged 6 years or older. Givinostat or placebo were administered in addition to a stable dose of corticosteroids throughout the study. Patients were recruited into 2 groups:

- Group A (120 Patients): subjects with a baseline VL MFF in the range > 5% and ≤ 30%, as assessed by MRS.
- Group B (59 Patients): subjects with baseline VL MFF outside of the above range (other criteria were the same).

A weight-based dose treatment regimen was applied. The starting dose was initially 17.7–62 mg oral givinostat twice a day, with a reduced dose of 11.8–41.4 mg twice a day. The protocol was then amended to reduce the starting dose for new participants, to 11.8–41.4 mg twice a day, allowing a further dose reduction of 9.4–33.1 mg twice a day.
The primary endpoint in Group A (pre-specified primary analysis population) was the change of time to complete 4 stairs climb (4SC) at 18 months.

The primary endpoint was met, givinostat significantly (p=0.035) reduced the decline in 4SC compared to placebo based on the prespecified log scale analysis (Table 4). When the results were analysed in non-log scale, the mean 4SC increased by 1.25 seconds in the givinostat group vs 3.03 seconds in the placebo group (see Table 4). Therefore, the treatment effect (change from baseline, givinostat minus placebo) was -1.78 seconds (p=0.037).

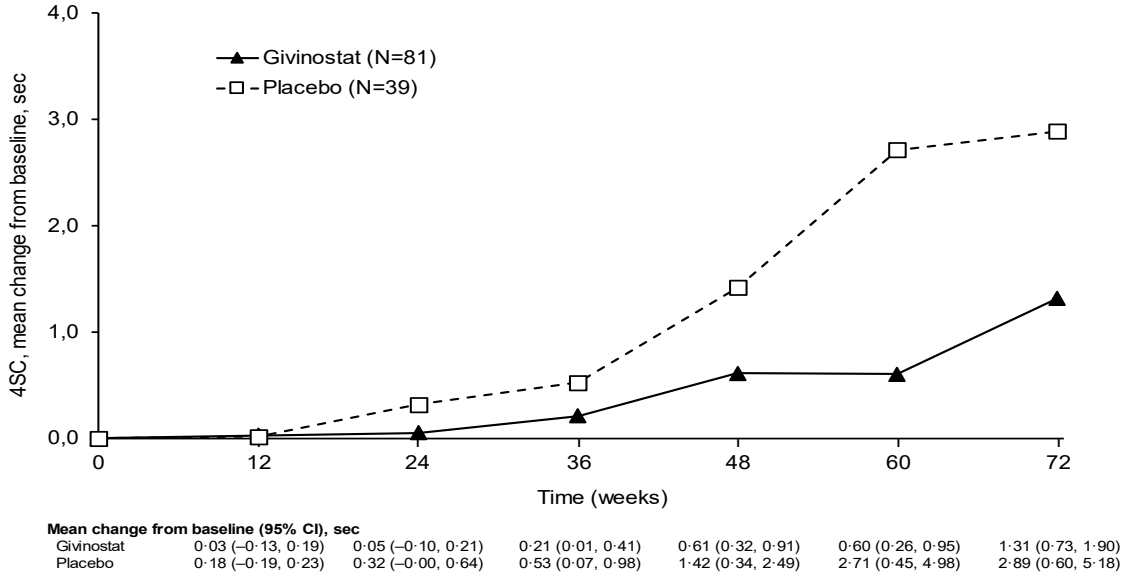
Table 4 – EPIDYS Study: Time (Seconds) to 4SC, Change from Baseline to 18 Months (Group A)

Time to 4SC	Givinostat[§] (N = 81)	Placebo[§] (N = 39)
Log Scale Analysis*		
GLS mean (log scale SE) (95% CI)	1.27 (0.040) (1.172, 1.372)	1.48 (0.058) (1.317, 1.657)
GLS mean ratio (givinostat/placebo) (log scale SE) (95% CI) p-value	0.86 (0.071) (0.745, 0.989) 0.0345	
No Log Scale Analysis		
LS mean (95% CI)	1.25 (0.311, 2.181)	3.03 (1.666, 4.394)
Difference in LS means (givinostat-placebo) (95% CI) p-value	-1.78 (-3.462, -0.106) 0.0374	

*Log Scale analysis was performed since data were not normally distributed.
§ Givinostat or placebo were administered in addition to a stable dose of corticosteroids throughout the study.
Note: LS Means, CIs, and p-values are obtained from an analysis of covariance (ANCOVA) model on change from baseline in 4SC at Month 18.
GLSmean change from baseline should be interpreted as a rate change (EOS/baseline).

Figure 1 describes the observed mean time to 4SC during the 72 weeks of treatment in the two groups.

Figure 1 – Study 48: Observed Mean Change in Seconds to 4SC by Treatment Over Time (Group A)

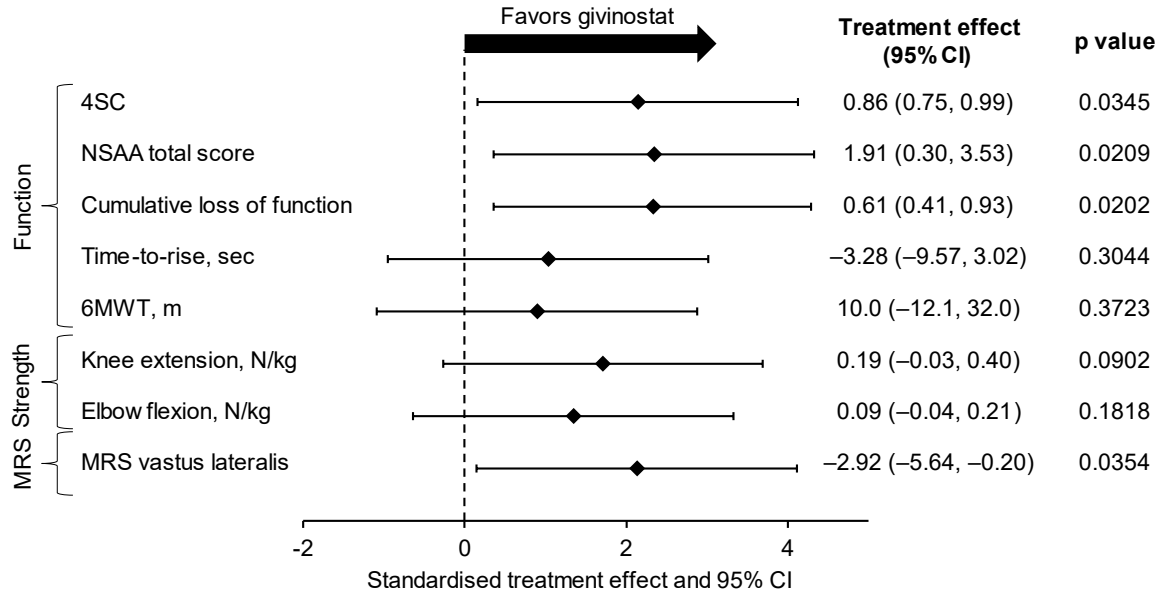


*Givinostat or placebo were administered in addition to a stable dose of corticosteroids throughout the study.

The key secondary efficacy endpoints in Group A were the change from baseline to 18 months in physical function assessed by North Star Ambulatory Assessment (NSAA), time to rise from floor (TTR); distance walked in 6 minutes (6MWT); muscle strength evaluated by knee extension and

elbow flexion as measured by hand-held myometry (HHM); and fat fraction of vastus lateralis muscles evaluated by Magnetic Resonance Spectroscopy (MRS) technique. Overall, the results of the key secondary endpoints assessing function, strength and muscle morphology did not reach formal statistical significance based on the pre-specified Hochberg analysis, however all outcomes were in favour of givinostat (Figure 2).

Figure 2 – EPIDYS Study: Primary and Key Secondary Efficacy Endpoints of Givinostat Versus Placebo (Group A)[§]



[§] Givinostat or placebo were administered in addition to a stable dose of corticosteroids throughout the study.

Givinostat long term safety, tolerability and efficacy are evaluated in an ongoing prospective open label, long-term extension (OLE) study named STUDY 51. Patients who completed the givinostat phase 2 trial (STUDY 43) and patients who completed the givinostat phase 3 trials (EPIDYS) were enrolled in STUDY 51. Additionally, 30 givinostat naïve patients were also enrolled in the OLE cohort. In total, 207 male patients were enrolled and receive givinostat with a weight-based dose regimen that ranges from 9.4 mg twice daily to 62 mg twice daily. All patients were on a stable dose of corticosteroids before enrolling and continue corticosteroid treatment throughout the study.

The benefit/risk of givinostat in the absence of concomitant corticosteroid treatment in DMD patients has not been determined.

The benefit/risk of givinostat in non-ambulatory patients has not been determined.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Duvyzat in one or more subsets of the paediatric population in DMD.

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Absorption

Givinostat is well absorbed after oral administration. Mean plasma concentrations increase in a dose-proportional manner, and maximum plasma concentrations are achieved about 2-3 hours after administration. A high fat standard meal resulted in some increase in the exposure (about 30% increase in area under the plasma concentration-time curve [AUC] and about 20% increase in maximum plasma concentration [C_{max}]) and a delay in time to maximum concentration (T_{max}) from 2 to 3 hours. Steady-state concentrations are achieved within 5 to 7 days after both once a day and twice a day dosing. A moderate accumulation of less than 2-fold was observed after twice daily administration.

A physiologically based pharmacokinetic analysis, including healthy volunteer data, predicted an oral bioavailability in humans ≥ 50% after single oral administration at the dose range of 44.3 to 177.2 mg.

Distribution

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

Biotransformation

In vitro studies with human enzymatic preparations together with animal metabolism *in vitro* and *in vivo* showed that givinostat is extensively metabolised forming several metabolites. CYP450 and UGTs are not involved in the main metabolic reactions. The enzymes forming the primary metabolites have only been partially identified. Four major metabolites, which are inactive, have been characterized in humans and animal species, although with differences in quantitative amounts.

Elimination

In plasma, givinostat displays a bi-phasic elimination profile with a mean apparent terminal elimination phase (half-life) of about 6 hours. The elimination of givinostat is likely dependent on metabolism followed by renal and biliary excretion. Urinary excretion of givinostat and the main metabolites in humans has been evaluated in healthy volunteers after single and repeated doses of givinostat. The percentage of unchanged givinostat recovered in urine was very low after both single and repeated twice daily administration (< 3% of the dose).

Linearity/non-linearity

The pharmacokinetics of givinostat is linear, since the AUC_{∞} obtained after single administration is comparable to that with repeated once daily administration, with a possible minimal apparent accumulation of active substance over time (range of accumulation ratios found 1.0 - 1.7).

Linearity was tested after single administration of doses 44.3 to 354.4 mg and multiple administration of doses 44.3 to 177.2 mg.

Weight

Based on the population PK analyses, weight resulted to significantly affect givinostat clearance. The effect is not linear, i.e., the effect is larger at smaller weights and smaller in weights 30 kg and above. Thus, a weight-based dose is recommended.

Characteristics in specific groups

The population PK analyses show that age or co-administration with corticosteroids has no effects on the pharmacokinetics of givinostat.

The pharmacokinetics of givinostat have been evaluated in male paediatric DMD patients from 6 years old.

Hepatic impairment
Givinostat has not been studied in patients with hepatic impairment. Caution should be exercised in the administration and monitoring of the product in these patients.

Renal impairment
Givinostat has not been studied in patients with renal impairment. However, renal impairment is not expected to impact the exposure of givinostat because renal excretion is not a significant route of givinostat elimination.

5.3 Preclinical safety data

In repeated dose oral toxicity studies in rats and monkeys, a dose dependent decrease in white blood counts with related atrophy of lymphoid organs (thymus, lymph nodes and spleen), in red blood cell and platelet counts, and in cellularity in the bone marrow was seen with givinostat. An increase in liver enzymes was also observed. In monkeys, bile duct hyperplasia was additionally induced. These toxicities were generally reversible upon drug discontinuation, but developed at lower givinostat exposures in animals than achieved at the maximum recommended human dose (MRHD).

Genotoxicity and carcinogenicity
Givinostat was positive for frameshift mutations at high doses *in vitro* in bacteria (Ames test), negative in mammalian cells (TK+/- in mouse lymphoma cells), and negative *in vivo* in transgenic BigBlue rats and in the Pig-a locus.
In conclusion givinostat does not pose a relevant genotoxic potential *in vivo*.

No data from carcinogenicity studies with givinostat are currently available.

Reproductive and developmental toxicity
Givinostat caused dose-dependent decreases in size and weight of male accessory organs already starting at the lowest dose. Mid and high dose animals showed an increase of the pre-coital interval and lower amounts of copulation plugs probably resulting from disturbance on ejaculate formation. However, sperm parameters and number of pregnant females were not affected.

Maternal adverse effects were observed at the high dose levels in the embryo-foetal and in the pre- and postnatal development toxicity studies. Effects on gestation, embryo-foetal development and litter parameters were considered secondary to maternal toxicity. However, effects on embryo-fetal development and litter parameters were already observed at mid dose levels in the rat and rabbit embryo-fetal development study as well as in the low dose group of the pre-/postnatal development study. There was no adverse effect on offspring behaviour, neurological growth, sexual maturation and reproductive function.
Overall, effects on reproductive toxicity were observed at lower givinostat exposures in animals than achieved at the MRHD, except for the embryo-foetal development study in rabbits with a safety margin of about 10 towards human exposure at the MRHD.

Juvenile toxicity
In rats, some effects were observed on haematological parameters and lymphoid organs at the high dose levels, which were fully or partially reversible. These effects were observed at lower givinostat exposures in animals than achieved at the MRHD. No treatment-related effects on animal growth, sexual maturation, reproductive performances, and in neurobehavioural development were observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 20 (E432)
Glycerol (E422)
Tragacanth gum (E413)
Sodium benzoate (E211)
Peach flavour: natural flavouring substances, flavouring substances, propylene glycol (E1520)
Cream flavour: natural flavouring substances, flavouring substances, propylene glycol (E1520)
Saccharin sodium (E954)
Liquid sorbitol (E420)
Tartaric acid (E334)
Sodium hydroxide (E524)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
After first opening: 60 days.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

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.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Italfarmaco S.p.A.
Viale F. Testi, 330
20126 Milano
Italy
Tel: +39 02 64431
info@italfarmacogroup.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1930/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Italfarmaco S.A.
San Rafael, 3
28108 Alcobendas
(Madrid) Spain

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of givinostat in the treatment of Duchenne Muscular Dystrophy in ambulant patients, aged 6 years and older, and with concomitant corticosteroid treatment, the MAH should conduct and submit the results of a randomised, double blind, placebo-controlled study in ambulant patients with Duchenne Muscular Dystrophy, according to an agreed protocol.	31 July 2033
In order to confirm the long-term efficacy and safety of givinostat in the treatment of Duchenne Muscular Dystrophy in ambulant patients, aged 6 years and older, and with concomitant corticosteroid treatment, the MAH should conduct and submit the final results of a non-interventional study based on data from sites and/or patient registries, according to an agreed protocol.	Final report: December 2037

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Duvyzat 8.86 mg/ml oral suspension
givinostat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 8.86 mg givinostat (as hydrochloride monohydrate)

3. LIST OF EXCIPIENTS

Also contains: sodium benzoate (E211) and sorbitol (E420) See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral suspension
Bottle of 140 ml with a 5 ml graduated dosing syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

Shake, by turning the bottle up and down approximately 40 times, for at least 30 seconds until the liquid is homogeneous

Scan here for package leaflet or visit www.duvyzat.eu

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:
Once opened, use within 60 days
Date of first opening:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Italfarmaco S.p.A.
Viale F. Testi, 330
20126 Milano
Italy
Tel: +39 02 64431
info@italfarmacogroup.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1930/001

13. BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Duvyzat

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Duvyzat 8.86 mg/ml oral suspension
givinostat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 8.86 mg givinostat (as hydrochloride monohydrate)

3. LIST OF EXCIPIENTS

Also contains: sodium benzoate (E211), and sorbitol (E420)
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral suspension
140 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
See leaflet before use
Shake before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:
Once opened, use within 60 days

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Duvyzat 8.86 mg/ml oral suspension
givinostat

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Duvyzat is and what it is used for

Duvyzat contains the active substance givinostat.

It is used to treat Duchenne muscular dystrophy (DMD) in patients aged 6 years and older, who are able to walk and are under steroid treatment.

DMD is caused by mutations in the DMD gene. These changes in the gene compromise muscle cells function and lead to muscle progressive degradation.
By blocking the activity of HDAC enzymes in the muscle cells, Duvyzat prevents muscle degradation.

2. What you need to know before you take Duvyzat

Do not take Duvyzat
- If you (or your child) are allergic to givinostat or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before taking Duvyzat.

Duvyzat lowers the number of blood cells in your blood, most notably the number of blood platelets responsible for clotting of the blood (a condition known as thrombocytopenia).
Your doctor will check your blood for levels of platelets before treatment and regularly during the entire course of treatment with Duvyzat.
Your doctor may reduce your dose to increase your platelet count or stop treatment with Duvyzat if thrombocytopenia continues.
Inform your doctor if you notice any unexpected bleeding.

Duvyzat may be associated with increased levels of fats (triglycerides) in your blood.
Your doctor will do blood tests before you start Duvyzat and regularly during treatment to check your triglyceride levels.
The dose of givinostat may be reduced in case of persistent increase in levels of fats (triglycerides) in your blood.
Your doctor may stop treatment if the levels of fats in your blood (triglycerides) do not decrease despite dietary measures and dose reductions.

You may experience diarrhoea and vomiting while taking Duvyzat.
Your doctor may adjust the dose of Duvyzat based on severity of diarrhoea or stop treatment if diarrhoea and vomiting do not improve.
Your doctor might consider the use of medicines to treat vomiting, diarrhoea and to avoid excessive loss of fluids.

High doses of Duvyzat (5 times higher than the recommended dose) may cause an irregular heartbeat.
Your doctor will consider if you can use Duvyzat when there is an increased risk for abnormal heartbeat, abnormal mineral levels in your body or concomitant use of other medicines.
Your doctor may check your heart function when starting Duvyzat if you have an underlying heart problem or if you use medicines that can cause irregular heartbeat.
Your doctor may consider to stop treatment with Duvyzat if your heartbeat is found irregular.

Contact your doctor, who may stop your therapy with Duvyzat, if any of the above conditions appear.

Other medicines and Duvyzat
Tell your doctor if you are taking, have recently taken, or might take any other medicines.

Duvyzat may increase the risk of side effects of some other medicines by increasing the amount of these medicines in the blood. Some of these medicines include:
- carbamazepine, phenytoin (a medicine used to treat epilepsy),
- amitriptyline (a medicine used to treat low mood and depression),
- digoxin (a medicine used to treat heart failure and abnormal heart rhythms),
- metformin (a medicine to control type II diabetes),
- amiloride (a medicine used to treat high blood pressure),
- histamine type 2 receptor antagonists (a medicine used to treat duodenal and gastric ulcers and common heartburn).

Caution is advised when Duvyzat is administered with medicinal products known to cause abnormal heartbeat.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. If you become pregnant while taking Duvyzat, consult your doctor immediately. Use of Duvyzat should be avoided while you are pregnant or breast-feeding.

Driving and using machines
This medicine may cause dizziness or tiredness. If you feel dizzy or tired, do not drive or use machines.

Duvyzat contains sorbitol, sodium benzoate and sodium

Sorbitol:

This medicine contains 400 mg sorbitol in each ml.
Sorbitol is a source of fructose. If your doctor has told you that you (or your child) have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you (or your child) take or receive this medicine.

Sodium benzoate:
This medicine contains 4.4 mg sodium benzoate in each ml.
Sodium benzoate may increase jaundice (yellowing of the skin and eyes) in new born babies (up to 4 weeks old).

Sodium:
This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

3. How to take Duvyzat

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Duvyzat should be taken by mouth, using a syringe. It should be taken two times per day. The recommended dose of Duvyzat depends on your body weight, as shown in the Table 1.

Table 1 – Recommended Dose

Weight (kg)	Duvyzat oral suspension volume to be taken twice daily
≥ 15 and < 20	2.5 ml
≥ 20 and < 40	3.5 ml
≥ 40 and < 60	5.0 ml
≥ 60	6.0 ml

If your prescribed dose is more than 5 ml per dose, you can use the same oral syringe more than once.

Your dose may need to be lowered (see Table 2) by your doctor if certain symptoms appear (see Warnings and precautions):
- decreased platelet count;
- moderate or severe diarrhoea (more than 4 stools per day);
- increased levels of fats in your blood.

Table 2 – First dose reduction

Weight (kg)	Duvyzat oral suspension volume to be taken twice daily
≥ 15 and < 20	2.0 ml
≥ 20 and < 40	2.5 ml
≥ 40 and < 60	3.5 ml
≥ 60	4.5 ml

If the above abnormalities do not improve, your doctor may further reduce your dose (see Table 3).

Table 3 – Second dose reduction

Weight (kg)	Duvyzat oral suspension volume to be taken twice daily
≥ 15 and < 20	1.5 ml
≥ 20 and < 40	2.0 ml
≥ 40 and < 60	3.0 ml
≥ 60	4.0 ml

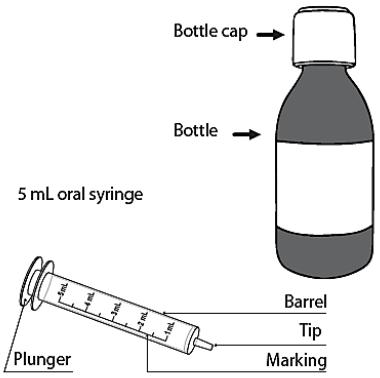
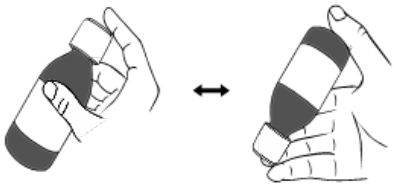
If these abnormalities still persist or if you experience irregular heartbeat, your doctor may consider stopping treatment with Duvyzat.

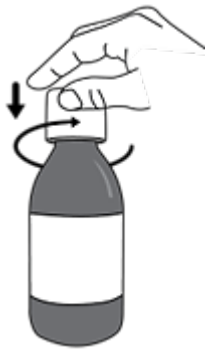
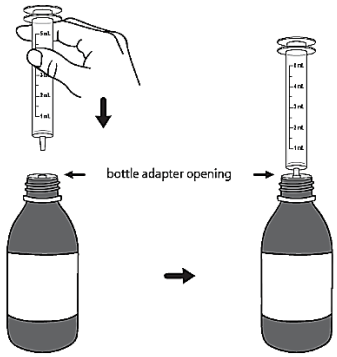
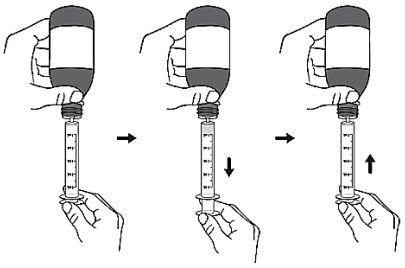
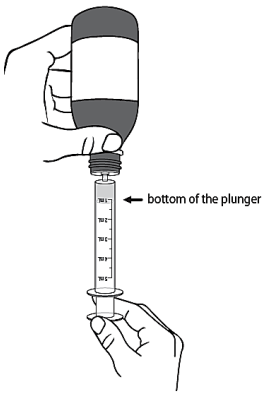
Method of administration

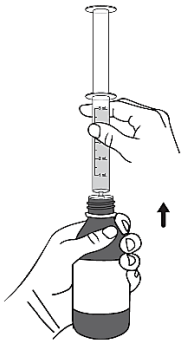
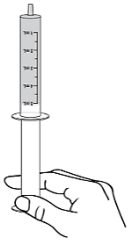
Duvyzat is for oral use.
The oral suspension must be shaken by hand approximately 40 times for at least 30 seconds by continuously turning the bottle up and down until the oral suspension is mixed well and looks the same throughout.
The suspension is dosed by using the graduated oral syringe.

Important information about dosing Duvyzat:
Ask your doctor or pharmacist to show you how to measure your prescribed dose.

- Take Duvyzat as prescribed by your doctor (see Tables 1, 2, 3);
- The recommended dose of Duvyzat is taken by mouth 2 times per day;
- Take Duvyzat as it is (not to be diluted in/with water or other liquids);
- Take Duvyzat with food to reduce the bitter taste of givinostat;
- Always take Duvyzat using the oral syringe (5 ml) provided with the medicine.

First time use of bottle only: Remove Duvyzat bottle and the 5 ml oral syringe from the carton (see Figure A).	 **Figure A**
Step 1. Make sure the bottle is closed properly and shake the bottle approximately 40 times **for at least 30 seconds** by continuously turning the bottle up and down (see Figure B). Stop when the Duvyzat oral suspension is mixed well and looks the same throughout.	 **Figure B**

Step 2. Open the bottle by pressing down on the bottle cap and turning it to the left (counter-clockwise) (see Figure C). Do not throw away the bottle cap.	 **Figure C**
Step 3. **For first time use only:** Take the provided oral syringe to be used and firmly insert the tip of the oral syringe into the bottle adapter opening (see Figure D). **For all other uses:** Take the provided oral syringe to be used, push the plunger all the way down (to remove the air) and firmly insert the tip of the oral syringe into the bottle adapter opening (see Figure D).	 **Figure D**
Step 4. While holding the oral syringe in place, turn the bottle upside down. Slowly pull the plunger down to pull back a small amount of the suspension. Then push the plunger all the way up to remove any air bubbles (see Figure E).	 **Figure E**
Step 5. Slowly pull the plunger down until the bottom of the plunger is even with the markings on the oral syringe for the prescribed dose of Duvyzat (see Figure F). If your prescribed dose is more than 5 ml, you will need to use the same oral syringe more than one time.	 **Figure F**

Step 6. While keeping the plunger in the same position, turn the bottle upright, and place it carefully on a flat surface. Remove the oral syringe by **gently** twisting or pulling it out from the bottle adapter opening. **Do not** hold the oral syringe by the plunger because the plunger may come out (see Figure G). Take or give Duvyzat right away after it is drawn up into the oral syringe. **Do not store** the filled oral syringe.	 **Figure G**
Step 7. Check that the prescribed volume (ml) of Duvyzat has been drawn up into the oral syringe (see Figure H). Figure H shows an example of a 5 ml dose. Your dose may be a different volume.	 **Figure H**
Step 8. The child or adult should sit upright to take a dose of Duvyzat. Place the tip of the oral syringe against the inside of the cheek. Slowly push the plunger all the way down until there is no more medicine left in the oral syringe. If your prescribed dose is more than 5 ml, repeat Step 3 through Step 8 to give the remaining part of the dose.	
Step 9. After use, replace the bottle cap and turn the bottle cap to the right (clockwise) to close the bottle (see Figure I).	 **Figure I**
Step 10. Wash the oral syringe in water and allow to dry. Store the oral syringe in a clean, dry place.	

If you take more Duvyzat than you should
Contact your doctor or a hospital if you take more than the prescribed dose of Duvyzat.
Your doctor will decide what care should be provided. This may include checking your heart function.

If you forget to take Duvyzat
It is important to take the correct dose.
If you forget a dose, take the next dose when needed.
Do not take a double dose to make up for a forgotten dose.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

If you stop taking Duvyzat
Do not stop taking Duvyzat without talking to your doctor.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
You may have one or more of the following side effects after taking Duvyzat:

Very common side effects (may affect more than 1 in 10 people):
- belly (abdominal) pain
- decrease in blood platelet count (thrombocytopenia)
- diarrhoea
- elevated levels of blood fats (hypertriglyceridaemia)
- fever (pyrexia)
- vomiting

Common side effects (may affect up to 1 in 10 people):
- anxiety
- constipation
- decreased appetite
- dizziness
- skin redness (erythema)
- tiredness (fatigue)
- diarrhoea and vomiting (gastroenteritis)
- collection of blood under the skin (haematoma)
- increased thyroid stimulating hormone (TSH) levels in blood
- joint pain (arthralgia)
- muscle pain (myalgia)
- muscular weakness
- rash

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Duvyzat

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the carton and bottle after "EXP". The expiry date refers to the last day of that month.

Once opened, use within 60 days.
Discard any unused Duvyzat oral suspension remaining after 60 days of first opening of the container.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Duvyzat contains
The active substance is givinostat.
Each ml of oral suspension contains 8.86 mg givinostat (as hydrochloride monohydrate).

The other ingredients are: polysorbate 20 (E432), glycerol (E422), tragacanth gum (E413), sodium benzoate (E211), peach flavour (natural flavouring substances, flavouring substances, propylene glycol E1520), cream flavour (natural flavouring substances, flavouring substances, propylene glycol E1520), saccharin sodium (E954), liquid sorbitol (E420), tartaric acid (E334), sodium hydroxide (E524), purified water.

What Duvyzat looks like and contents of the pack
Duvyzat is a white to off-white or faintly pink oral suspension.
Pack of one bottle of 140 ml.
The bottle is packed with one 5 ml graduated oral syringe. The oral syringe is graduated from 1 to 5 ml by increments of 0.5 ml.

Marketing Authorisation Holder
Italfarmaco S.p.A.
Viale F. Testi, 330
20126 Milano
Italy

Manufacturer
Italfarmaco S.A.
San Rafael, 3
28108 Alcobendas (Madrid)
Spain

Scan the code with a mobile device to get the package leaflet in different languages.

Or visit the URL https://www.duvyzat.eu

This leaflet was last revised in MM/YYYY

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine. The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

Annex IV

Conclusions on the granting of the conditional marketing authorisation and presented by the European Medicines Agency

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.

- **Similarity**

The CHMP is of the opinion that Duvyzat is not similar to authorised orphan medicinal product(s) within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000 as further explained in the European Public Assessment Report.