GIVINOSTAT FOR DUCHENNE MUSCULAR DYSTROPHY: Clinical monitoring guidance

The following guidance is based on the EPIDYS study and the summary of product characteristics (SmPC) (MHRA Products | Product results). **It is designed to support clinical decisions, by providing a standardised protocol for the use and monitoring of givinostat in DMD, based on the available evidence and while waiting for further feedback from NICE and MHRA**. This guidance **does not constitute formal clinical guidelines, and each patient needs to be assessed and managed on a case by case basis by the treating clinician.** Finally, the guidance is not intended to promote the prescription of givinostat in DMD – this is a decision that remains with the individual clinician.

This document complements the givinostat summary of SmPC and patient information leaflet released by the MHRA (MHRA Products | Product results)

This document will be updated regularly as new evidence on the safety and efficacy profile of givinostat in DMD emerges.

Specific questions for the drug developer, Italfarmaco can be sent to:
UK.Medical.Information@italfarmacogroup.com

INDICATION

Givinostat received conditional marketing authorization from the MHRA in December 2024 with the following indication:

Givinostat is indicated for patients with Duchenne muscular dystrophy (DMD) aged 6 years and older. The MHRA authorization does not specify any restriction related to the ambulatory status.

The inclusion criteria listed below refer to **the ambulant EAP for givinostat** as defined by national agreement within the paediatric North Star Centre Network and in line with the definition of "ambulation" applied for Translarna MAA.

A non-ambulant EAP for givinostat is currently open in the UK. Following discussion within the North Star Network, it was felt that at present, there is insufficient evidence on the risk-benefit of givinostat in non-ambulant patients. However, the implementation of any EAP is made at the discretion of individual clinicians and their hospitals. If your hospital has agreed to support the non-ambulant EAP, the ambulatory inclusion criteria listed below will *not* apply. However the other criteria and information reported in this document *can* still apply.

Please note, the NICE application for the reimbursement of givinostat is limited to ambulant patients. NICE might mandate specific inclusion and exclusion criteria for access to reimbursed drug, which have not yet been released.

Finally, there is an ongoing MHRA review following recent safety reports, including three fatal cases, about patients treated with givinostat worldwide.

This guidance is therefore an ***interim document*** while waiting for NICE and MHRA feedback.

INCLUSION CRITERIA – (ambulant EAP for givinostat)

- Confirmed diagnosis of DMD
- Aged 6 years and above
- Ambulant[a], defined as able to walk or stand, even with support
- Residing lawfully in the UK on a properly settled basis

EXCLUSION CRITERIA

- Platelets < 150 x 10^9/L at baseline
- QTcB (Bazetts) ≥ 460 ms or QTcF (Fridericia formula) > 450 ms at baseline [b, c]
- Fasting triglycerides[d] ≥ 300 mg/dl (3.42 mmol/l)
- Participation in an ongoing clinical trial (based on study-by-study and following discussion with the Sponsor of the trial)
- Hereditary fructose intolerance and/or sorbitol intolerance

[a] Patients must be ambulant (as defined above) when they first start treatment with givinostat. If patients become non-ambulant after having started givinostat, they can remain in the Ambulant EAP.

[b] The clinical trial for givinostat specified QTcF (Fridericia formula) > 450 ms as exclusion criteria. However, most ECG machines provide an automated QTc-interval (ms) measurement – typically using Bazett's formula (QTcB). Therefore both values are provided here as a reference.

[c] All patients with QTcB > 440 ms should be discussed with a cardiologist who can manually calculate QTcF, can compare QTc on previous ECGs and review concomitant medication, to assess risk of QTc prolongation and cardiac arrhythmia (see *Cardiac monitoring of DMD patients starting givinostat medication*)

[d] Triglycerides should be tested in fasting condition (≥ 6 hours) if possible. If not, test non-fasting:
- If non fasting triglycerides ≤ 300 mg/dl (≤ 3.42 mmol/L): no further action
- If non fasting triglycerides > 300 mg/dl (> 3.42 mmol/L): repeat in fasting conditions to confirm eligibility

If triglyceride exclusion criteria are met, the patient should receive dietary advice and could be reconsidered for treatment at a later stage at the clinician's discretion.

CONTRAINDICATIONS

Hypersensitivity to the active substance or any excipients, including sorbitol (or fructose), peach and cream flavour (see section 6.1 on the SmPC for the full list of excipients: MHRA Products | Product results

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Givinostat can cause dose-related thrombocytopenia (and much less frequently other signs of myelosuppression, including decreased haemoglobin and neutropenia). Patients with low baseline PLT might have a higher risk to meet the threshold for dose modification or dose interruption. Closer follow up at the beginning of treatment and/or individualised adjustment of the threshold might be considered in individual cases.

The weight dose bands implemented within the EAP are broader than the bands used in clinical trials with givinostat (nine dose bands in the clinical trials versus four dose bands in the EAP). Therefore, patients with body weight at lower levels within the band might be at a higher risk of developing dose-dependent adverse reactions.

In healthy volunteers, higher doses of givinostat caused modest QTcF prolongation. This has not been observed in patients with DMD treated with givinostat within the clinical trials. However, caution should be applied when patients are taking any other drugs known to prolong the QTc (examples of such drugs: anti-psychotic such as risperidone or methylphenidate; antibiotics such as azithromycin, clarithromycin, ciprofloxacin; antiemetics such as ondansetron), or over-the-counter medicines (e.g. antihistamines such as famotidine) (see Cardiac monitoring link above)

As per 20 Oct 2025, three cases of sudden death have been reported in children and teenagers with DMD treated with givinostat. An investigation by Italfarmaco has concluded that there is no direct causality between the deaths and givinostat use. Of note, all three cases shared co-morbidities and concomitant medications that could have increased the risk of sudden cardiac death, either independently or in combination with givinostat. Moreover, there is no data and only limited clinical experience with givinostat in older patients with DMD. These cases have been reported to the MHRA and they are currently under review. While waiting for the MHRA advice, and given that it is difficult to make a definitive recommendation on the current evidence, particular attention should be paid when considering givinostat treatment in patients with a higher risk of cardiac disease. This includes those with : significant cardiomyopathy, a previous history of arrhythmia or family history of sudden death/cardiac arrhythmia. A detailed history of all concomitant medications, particularly those known to prolong the QT interval or to be associated with sudden death (e.g. methylphenidate, risperidone, aripiprazole etc) must be taken to support an individual risk assessment for treatment and to guide closer monitoring.

Patients already treated with givinostat should be regularly reviewed for co-morbidities and concomitant medications. If there are any concerns, the risks of combination therapy should be discussed with a cardiologist, other relevant specialists (e.g. neuropsychiatrist) and families to ensure informed decision making.

Prescribing drugs which can also prolong the QT-interval is not an absolute contraindication (as per SmPC advice) in patients with DMD who are already taking givinostat. However, families should be informed about these possible pharmacological interactions and encouraged to check with their neuromuscular specialist and/or pharmacist before starting new medications. The use of an alternative drug that is not associated with prolongation of the QT interval should always be considered. When, after careful discussion with relevant specialists, the patient and their family, addition of a QT-prolonging drug is deemed to be in the patient's best interest, closer ECG monitoring and cardiac review must be put in place.

There is no information about the interaction between givinostat and Translarna or any of the exon skipping drugs available through compassionate use programmes the UK, including eteplirsen, casimirsen or golodirsen. Being on these drugs does not prevent the use of givinostat as part of the EAP, but risks and benefits should be discussed with patients and their families and closer monitoring might be required.

See also ***interaction with other medical products*** below**.**

DOSE

The recommended dose as per SmPC is based on the EPYDYS study. The EPYDYS trial included three dose bands (A, B and C). Approximately 60% of the patients enrolled in the EPYDYS study who received the higher dose (band A) experienced side effects which required dose reduction (to Band B or C) or treatment interruption. Based on this observation, the EPYDYS study protocol was amended and all subsequent studies with givinostat (Ulysses study in non-ambulant patients and the study enrolling younger, 2-6 year olds) have only included two dose bands (B and C).

As only 23 patients completed the 18-month EPIDYS study on the higher dose (Band A), the comparison between dose A and dose B in term of efficacy was limited; a trend towards a dose-response was observed, but the difference was not significant at 18 months.

Early experience in the EAP (as per October 2025) seems to be in line with the clinical trial findings, with approximately 60% of patients treated with the higher dose experiencing side effects (e.g. thrombocytopenia, diarrhoea) requiring dose reduction, treatment interruption or discontinuation (personal reports from prescribing centres, systematic data collection planned but not yet performed).

Risk factors which might be associated with a higher risk of adverse events requiring dose reduction or treatment interruption/discontinuation include low platelet count and high body weight at baseline.

Moreover, the weight dose bands implemented within the EAP are broader than the bands used in clinical trials with givinostat, so patients with body weight at the lower end of the dose band might have a higher risk of developing dose-dependent adverse reactions.

Having reviewed this evidence, the Duchenne Care UK Emerging Therapies WG and the NS steering committee recommend a change in dosing approach and advise that **treatment should be initiated at the 1st dose modification** (i.e. Dose B from the clinical trial) **(see table 1).**

Patients who have already been started on the higher dose under the EAP as per SmPc recommendations, with no adverse events requiring dose modification for three months, could continue on this dose (recommended doses as per SmPC to include the higher dose are provided at the end of this document in Supplementary Materials – Table 1S) .

Up-titration of the dose in patients starting on 1st dose modification who have no adverse reactions within the first three months of treatment or those in whom adverse events resolved quickly on 1st or 2nd dose modification, might be considered in individual cases after discussion with the family. However, these patients will need closer monitoring following dose increase, in line with that recommended at the time of treatment initiation.

Table 1: Recommended starting dose in patients 6 years of age and older for treatment of DMD (first dose modification)

Weight*	Dosage	Oral Suspension Volume
10 kg to less than 20 kg	17.7 mg twice daily	2 mL twice daily
20 kg to less than 40 kg	22.2 mg twice daily	2.5 mL twice daily
40 kg to less than 60 kg	31 mg twice daily	3.5 mL twice daily
60 kg or more	39.9 mg twice daily	4.5 mL twice daily

**Based on actual body weight*

- Givinostat is a suspension and is administered orally twice daily; it should be taken together with food (to mitigate the bitter taste of givinostat and increase absorption) and should not be diluted in water or other liquid
- Each dose of givinostat is based on body weight (see table 1). Weight should be monitored at baseline and every six months thereafter to inform dose adjustments based on body weight
- If a dose is missed, advise to take the next scheduled dose and DO NOT take double dose.
- Dose might be reduced in response to side effects (in particular, thrombocytopenia, increased triglycerides and diarrhoea) – see details below
- Once dose is reduced in response to a side effect likely related to givinostat, it should not be increased, unless other causes of the side effect have been identified
- Givinostat can be stopped suddenly with no specific side effects expected
- The bottle should be shaken (inverted by 180°) for at least 30 seconds before use to ensure even distribution of the drug within the liquid
- Dose should be measured using the 5ml syringe provided
- Bottles can be stored at room temperature (even when the bottle has been opened)
- Once open, the bottle can be used for up to 60 days

MONITORING

All monitoring visits and results should be recorded using the routine NS clinical forms (these have been updated to allow recording of givinostat prescription, dosing and dose adjustments in response to side effects). These must be completed as accurately as possible at each clinical follow up visit (every six months). Side effects and dose adjustments occurring in between clinical assessments should be recorded on the NS forms at the next clinical follow up visit.

Before starting givinostat (baseline assessment)

If the assessments listed below (for both efficacy and safety) have been performed within three months from treatment initiation with givinostat, they might be recorded as baseline assessments at the judgement of the NM clinician, if no significant changes in motor function and general health are reported[a].

Efficacy:

As per routine SoC:

- NSAA including timed function test (fully ambulant patients);
- FVC and PCF (all patients);
- PUL (all patients but particularly for patients in the "transition" state[b]) (where feasible)

If a patient is not able to complete any of the above assessments, the NM clinician can make the decision on how to best monitor efficacy over time in that specific patient.

Safety:

- Blood test (FBC, including PLT, triglycerides[c])
- ECG – to assess QTc (see Cardiac monitoring linked above and below)
- Medical assessment as per SoC

- Assessment of contra-indications to givinostat, including allergies, detailing concomitant medications and review of medical history (e.g. any history of arrhythmia and family history of sudden death/cardiac arrhythmia).

Follow up

Efficacy:

As per routine SoC:

- NSAA including timed function test (fully ambulant patients);
- FVC and PCF (all patients);
- PUL (all patients but particularly for patients in the "transition" state[b] or who have lost ambulation since starting treatment) (where feasible)

If a patient is not able to complete any of the above assessments, the NM clinician can make the decision on how to best monitor efficacy over time in that specific patient.

Safety: See Table 2

Families should be alerted about side effects from givinostat and possible symptoms (e.g. vomiting, diarrhoea, malaise, generalised tiredness, epistaxis, epigastric or abdominal pain). Closer monitoring might be required in the presence of symptoms or signs of side effects.

Closer monitoring of PLT (e.g. every two weeks for eight weeks) should be considered when a patient increases the dose (e.g. change dose band based on increased body weight).

Closer ECG monitoring should be considered if QTc is prolonged, but not at a level to meet the stopping criteria (see below); ECG should also be repeated when a patient increases the dose of givinostat or if another drug with QT-prolonging effects is prescribed at baseline, followed by an ECG2-4 weeks after starting treatment and every six months thereafter. Any ECG abnormality should be discussed with a cardiologist. See Cardiac monitoring of DMD patients starting givinostat medication.

Table 2 – Safety monitoring of DMD patients on givinostat

<table>
<tr><td></td><td>Baseline[a]</td><td colspan="8">Month 1</td><td colspan="4">Month 2</td><td>Month 3</td><td>Month 6</td><td>Ongoing</td></tr>
<tr><td rowspan="2">Platelets (FBC)</td><td rowspan="2">X</td><td>W 1</td><td>W 2</td><td>W 3</td><td>W 4</td><td>W 5</td><td>W 6</td><td>W 7</td><td>W 8</td><td rowspan="2">X</td><td rowspan="2">X</td><td rowspan="2">Every 3 months</td></tr>
<tr><td></td><td>X</td><td></td><td>X</td><td></td><td>X</td><td></td><td>X</td></tr>
<tr><td>Triglycerides[c]</td><td>X</td><td colspan="4">X[d]</td><td colspan="4"></td><td>X</td><td>X</td><td>Every 6 months</td></tr>
<tr><td rowspan="2">ECG</td><td rowspan="2">X</td><td>W 1</td><td>W 2</td><td>W 3</td><td>W 4</td><td colspan="4" rowspan="2"></td><td rowspan="2"></td><td rowspan="2">X</td><td rowspan="2">Every 6 months[f]</td></tr>
<tr><td></td><td colspan="3">X[e]</td></tr>
</table>

[a] *If any baseline assessment is available within three months before treatment initiation, they might not need to be repeated, provided no significant changes in motor function and/or general health are reported. However, ECG should be repeated at baseline if there is a history of additional cardiac risk including concomitant use of drugs that can prolong QT interval*

[b] *Patient able to stand but unable to walk and/or patients unable to complete the NSAA*

[c] *Triglycerides should be tested in fasting condition (≥ 6 hours) if possible. If not, test non-fasting:*
- If non fasting triglycerides ≤ 300 mg/dl (≤ 3.42 mmol/L): no further action
- If non fasting triglycerides > 300 mg/dl (> 3.42 mmol/L): repeat in fasting conditions to confirm safety

[d] *Triglycerides should be repeated once during the first month after treatment initiation*
[e] *ECG should be repeated once, between week two and week four from treatment initiation (see Cardiac monitoring linked above)*
[f] *ECG monitoring every six months should be aligned with the cardiac follow up as per SoC. However, families should be advised to report changes in concomitant medications in between visits to monitor for possible drug interactions.*

DOSE MODIFICATIONS

Givinostat dose should be reduced if any of the following occur (see further details below):

- Platelet count <150 x 10^9/L (but ≥ 75 x 10^9/L) verified in two assessments one week apart – see figures 1 and 2 (without other explanation e.g. intercurrent infection)
- Moderate or severe diarrhoea (e.g. increase of ≥ 4 stools/day)
- Fasting triglycerides > 300 mg/dl (3.42 mmol/L) verified by two assessments approximately one week apart – see figures 3 and 4*

* If non-fasting triglycerides > 300 mg/dl (3.42 mmol/L), repeat in fasting conditions before taking action with givinostat dosing.

Dose should be reduced as per table 3 below**.

Treatment interruption prior to dosage modification might be considered, based on the severity of the adverse reactions.

If the adverse reaction persists after the dosage modification, givinostat should be discontinued.

Further details of dose modification recommendations based on specific adverse reactions are reported below.

Other adverse reactions might require dose modifications as per clinician's judgement.

As prolonged QTc was not observed in the clinical trials, there are no SmPC recommendations regarding dose reduction in response to an abnormal QTc. If the QTc is prolonged, but not at a level that meets the stopping criteria (QTcF > 500 ms or increase in QTcF > 60 ms from baseline at any time), the ECG should be repeated to confirm the abnormality and subsequent actions and monitoring discussed with a cardiologist.

**Please note, as per SmPc two dose modifications are allowed to manage adverse reactions. As we are now recommending starting treatment at the first dose modification described in the SmPC (starting dose = first dose modification) only one dose reduction will be allowed in case of adverse reactions, unless the dose has been increased/maintained at the SmPC starting level. If the adverse reaction persists after dose has been reduced to that defined as the SmPC 2nd dose modification, givinostat should be discontinued (see figures 1 and 3 for dose modification with regard to specific adverse reactions in patients started on the first dose modification).

For patients on the higher dose (either as started and maintained on the higher dose or post-dose increase), two dose reductions (to 1st and 2nd dosage modification) are allowed. Dose should be reduced to the first dose modification in response to an adverse reaction. If the adverse reaction persists after the first dosage modification, dose should be further reduced to the second dose modification as per table 4. If the adverse reaction persists after the second dose modification, givinostat should be discontinued (see figures 2 and 4 for dose modification with regard to specific adverse reactions in patients on the higher dose).

Table 3 – Dosage modification for adverse reaction in patients starting on 1st dose modification of givinostat

Weight*	Dosage	Oral Suspension Volume
10 kg to less than 20 kg	13.3 mg twice daily	1.5 mL twice daily
20 kg to less than 40 kg	17.7 mg twice daily	2 mL twice daily
40 kg to less than 60 kg	26.6 mg twice daily	3 mL twice daily
60 kg or more	35.5 mg twice daily	4 mL twice daily

**Based on actual body weight*

Table 4 – Dosage modification for adverse reaction in patients on the higher dose of givinostat

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

**Based on actual body weight*

STOPPING CRITERIA

Givinostat should be permanently stopped if the following occur:

- If an adverse reaction persists after dosage modification
- QTcF > 500 ms or increase in QTcF > 60 ms from baseline at any time
- PLT < 50 x 10^9/L (confirmed at repeated test) and/or if PLT ≥ 50 x 10^9/L but the patient presents with symptoms or signs of thrombocytopenia, without other identified causes
- Severe drug related diarrhoea (e.g. increase ≥ 7 stools/day)

Givinostat should be temporarily discontinued if the following occur:

- PLT ≥ 50 x 10^9/L but < 75 x 10^9/L (in the absence of symptoms)
- Fasting triglycerides ≥ 300 mg/dl (3.42 mmol/L)
- Moderate diarrhoea (e.g. increase ≥ 4 stools/day)

These criteria should be used as a guide, however the NM clinician should use their clinical judgement to decide whether treatment should be permanently or temporarily discontinued; for example, treatment interruption prior to dose modification might be considered in other circumstances rather than those listed, based on the severity and/or tolerability and acceptability of the adverse reaction.

Please note, once a "End of Treatment" treatment termination form is submitted for a patient, the patient will be automatically withdrawn from the Unipharm system. Therefore if, for whatever reason

a decision to restart medication is made at a later date, the patient will need to be re-registered through the Unipharm system which is not set up to be able to link to a previous registration number.

Therefore it is recommended not to submit the "End of Treatment" form until a final decision regarding treatment discontinuation has been made. Until then, treatment can be paused (temporarily interrupted). The Unipharm system will not flag any patients who have not had a recent order.

PLATELETS

- Givinostat may cause platelet (PLT) levels to drop, which may necessitate a dosage modification.
- Thrombocytopenia can be associated with bleeding events including epistaxis, hematoma or contusions.
- In the EPIDYS study, thrombocytopenia occurred in 33% of patients treated with givinostat and resulted in dose reduction in 28% of the patients. The maximum decrease in platelets occurred within the first two months of therapy and PLT levels than stabilised but remained low compared to baseline throughout the course of therapy.
- Givinostat must not be initiated in patients with a PLT count < 150 x 10^9/L. Other causes of PLT reduction should be excluded – e.g. PLT count can vary with intercurrent infections, so results should be confirmed on repeated test.
- PLT count must be monitored during treatment (see monitoring schedule, table 2) and the dose of givinostat should be modified in case of confirmed thrombocytopenia, without another identified cause (see figures 1 and 2).

Figure 1. Platelet count monitoring and dose modification in patients on givinostat started on the first dose modification

Figure 2. Platelet count monitoring and dose modification in patients on the higher dose of givinostat

TRIGLYCERIDES

- Givinostat can cause elevation in triglycerides, even in the absence of family history.
- In the EPIDYS study, hypertriglyceridemia (fasting triglycerides > 300 mg/dl or 3.42 mmol/L) occurred in 23% of patients treated with givinostat and led to treatment discontinuation in 2% of the cases and to dosage modification in 8% of the cases.
- Triglyceride levels must be monitored during treatment (see monitoring schedule, table 2) and the dose of givinostat should be modified in case of confirmed hypertriglyceridemia (see figures 3 and 4).
- Dietary advice should be provided at baseline and at each follow up appointment in clinic as per SoC, highlighting the increased risk of hypertriglyceridemia related to givinostat. Referral to a dietician might be considered on an individual basis as per treating clinician's judgement.
- If non-fasting triglycerides levels are > 300mg/dl, test should be repeated in fasting condition (at least 6 hours fasting). If fasting triglycerides > 300 mg/dl (3.42 mmol/l), results should be confirmed on repeated test in fasting conditions, in approximately one week. If fasting triglycerides persist > 300 mg/dl (3.42 mmol/l), dose of givinostat should be modified (see figures 3 and 4) and dietary advice provided.
- Treatment with givinostat should be discontinued if triglycerides remain elevated despite adequate dietary intervention and dose adjustment.

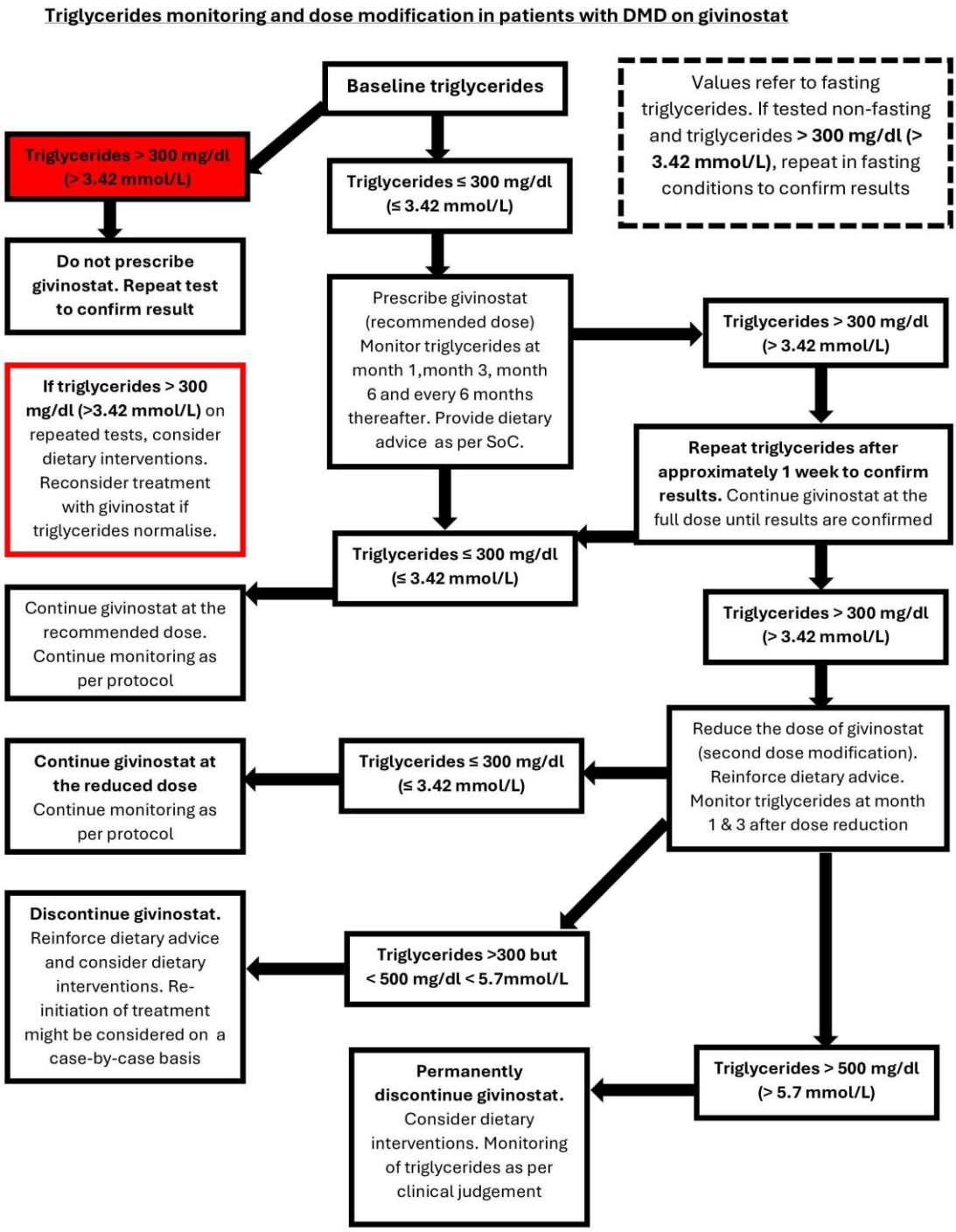

Figure 3: Triglycerides monitoring in patients on givinostat started on the first dose modification

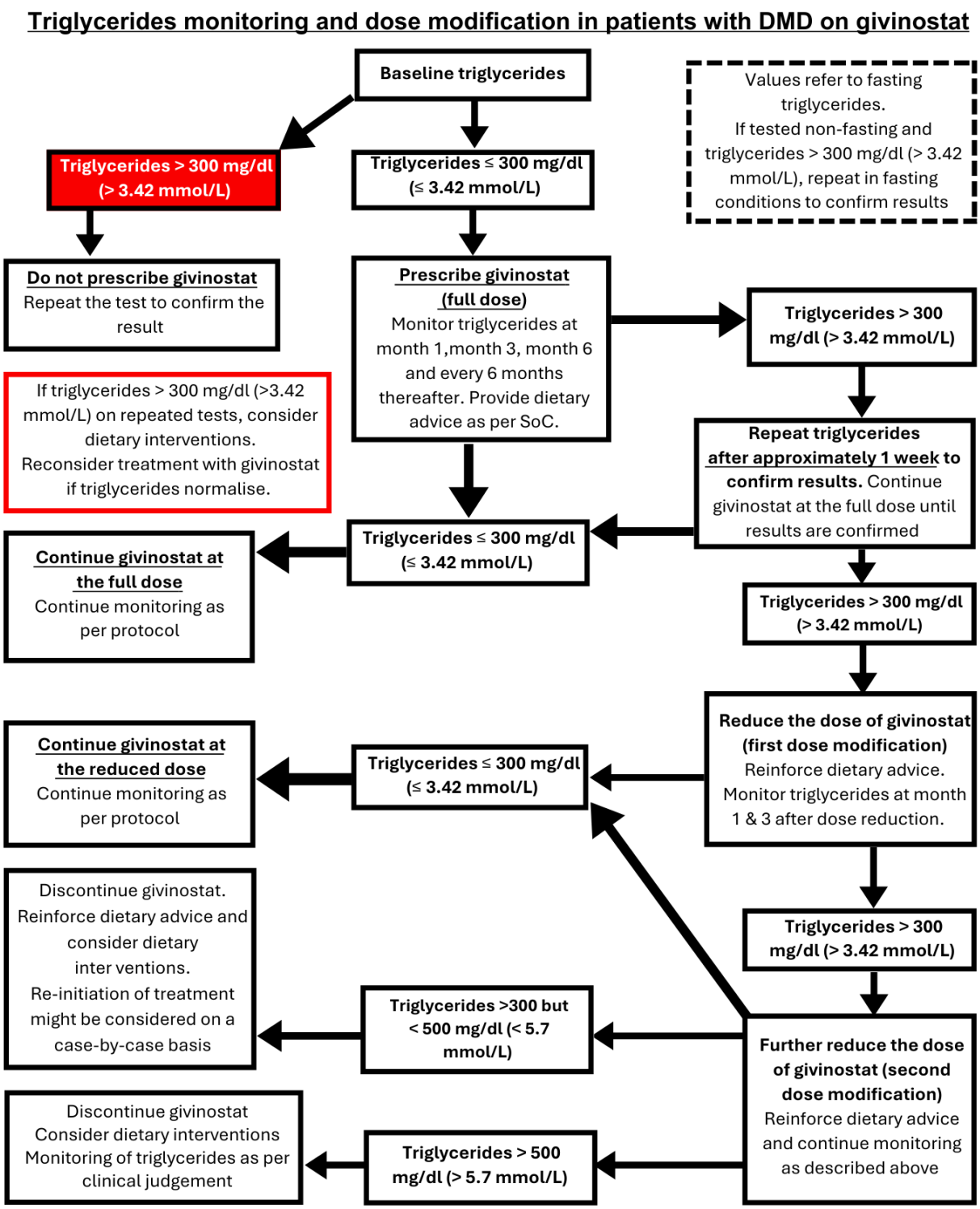

Figure 4: Triglycerides monitoring in patients on the higher dose of givinostat

DIARRHOEA and other gastrointestinal symptoms

- Gastrointestinal disturbances, including diarrhoea, nausea/vomiting, and abdominal pain are common adverse reactions to givinostat.
- In the EPIDYS study, diarrhoea was reported in 37% of patients treated with givinostat (and 20% of patients on placebo) however patients on givinostat reported many more episodes of diarrhoea (with one severe case reported) compared to placebo. Diarrhoea usually occurred within the first few weeks of initiation of treatment with givinostat. It was usually mild and resolved within two weeks.
- Vomiting and nausea was reported in 32% of patients treated with givinostat, usually occurring within the first two months of treatment.
- Abdominal pain occurred in 34% of patients treated with givinostat (and 25% of patients on placebo).
- Antidiarrheal medications may be considered during treatment with givinostat. While antiemetics (e.g. ondansetron) are not contraindicated, they should be prescribed with caution and taking into account their possible effect on QTc prolongation; alternative preparations might be considered (see Cardiac monitoring linked above).
- In the event of moderate/severe diarrhoea/vomiting, fluid and electrolytes should be replaced as needed to prevent dehydration. Treatment with hydrocortisone should be considered as per SoC (Wong et al., 2023).
- The dosage of givinostat in patients with moderate or severe diarrhoea should be reduced based on clinician and patient assessment of tolerability, and treatment should be discontinued if significant symptoms persist. As a guide, moderate diarrhoea (e.g. increase ≥ four stools/day) should trigger a dose reduction; treatment should be discontinued with severe diarrhoea (e.g. increase ≥ seven stools/day) or if moderate diarrhoea persists after dose reductions
- Treatment interruption prior to dosage modification might be considered.
- Other causes of diarrhoea and other gastrointestinal symptoms should be considered before dose reduction/discontinuation.

ADVERSE REACTION AND ADVERSE EVENTS REPORTING

As part of the EAP adverse reactions and adverse events need to be reported to Italfarmaco (ITF) using the provided Adverse Event form to: **UK.Medical.Information@italfarmacogroup.com**

Moreover, Healthcare professionals are asked to report any **suspected adverse reactions** via the Yellow Card Scheme - at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play and Apple App store.

All moderate/severe suspected adverse reactions (e.g. resulting in seeking medical advice, dose change) related (possibly/likely related) to givinostat must be reported. Key clinical information must be provided within the provided Adverse Event form.

All Serious Adverse Events, regardless their relation to givinostat, must be reported using the provided form, ideally within 24 hours from notification.

In case of Serious Adverse events (see definition below) all information required in the form should be reported.

Serious adverse event*: Serious adverse event is defined as an adverse event that results in significant clinical outcomes, including death, life-threatening situation, hospitalisation, disability, congenital anomaly, and other medically important events*.

INTERACTION WITH OTHER MEDICAL PRODUCTS

- Medical products that can prolong QT-interval should be prescribed with caution (seeMHRA Products | Search results for further details). These include drugs that might be relatively commonly prescribed in children and in patients with DMD such as over the counter antihistamines (e.g. famotidine), antibiotics (e.g. azithromycin, clarithromycin, ciprofloxacin), anti-psychotic (e.g. risperidone, methylphenidate), antiemetics (e.g. ondansetron), anaesthetics (e.g. propofol), class III antiarrhythmics (e.g. amiodarone). A comprehensive list of medical products that might cause QT-interval prolongation can be found on http://www.crediblemeds.org/
- Givinostat is a weak inhibitor of the renal uptake transporter OCT2. Closer monitoring of side effects of these drugs should be considered when givinostat is prescribed in combination with drugs known as a sensitive substrate of the OCT2 transporter (e.g.: metformin).
- Givinostat is a weak intestinal CYP3A4 inhibitor. Closer monitoring of side effects of these drugs should be considered when givinostat is prescribed in combination with orally administered CYP3A4 sensitive substrates (e.g. alfentanil, tacrolimus, sirolimus, lovastatin, simvastatin, indinavir, sildenafil, eletriptan, midazolam).
- There is no information about the interaction between givinostat and Translarna or any of the exon skipping drugs available through compassionate use programmes the UK, including eteplersen, casimirsen or golodirsen. Being on these drugs does not prevent using givinostat as part of the EAP but risks and benefits should be discussed with patients and their families and closer monitoring might be required.
- Other drug interactions remain unknown

CONSIDERATION ON GIVINOSTAT, SURGERY AND ANAESTHETICS

There is currently no clinical evidence to guide the use of givinostat in patients undergoing surgery and/or general anaesthesia. In the EPIDYS Phase III clinical trial, patients were excluded if they had undergone surgery that could have affected muscle strength or function within three months prior to study entry, or if they had planned surgery at any time during the study.

The following points outline key considerations for anaesthesia in patients treated with givinostat, based on its potential adverse effects (including thrombocytopenia, QT interval prolongation, and interactions with other medications that may prolong the QTc). Ultimately, the peri-operative management of patients receiving givinostat remains at the discretion and responsibility of the prescribing clinician, in collaboration with the relevant multidisciplinary team.

General principles regarding anaesthetic risk and pre-operative assessment in DMD continue to apply.

Also refer to the Association of Anaesthetists Great Britain and Ireland *Guidelines for the safe practice of total intravenous anaesthesia (TIVA) 2018*: **https://doi.org/10.1111/anae.14428**

Pre-operative considerations

- The potential increase anaesthetic risk associated with givinostat should be discussed as part of the anaesthetic consent process, in line with duty of candour requirements.
- Where possible, platelet count and ECG should be performed prior to surgery as part of the pre-operative work-up.
- Givinostat should be discontinued in advance of planned surgery. Given its approximate half-life of six hours, cessation at least 72 hours before surgery should be considered.
- The case should be discussed with cardiologists if appropriate given the patient history, and a plan to manage any peri-operative ventricular arrhythmias (VF/VT) should be made in advance, even though this is an unlikely event.

Anaesthetic considerations

- Propofol possible adverse effects include bradycardia, and there is some published evidence to suggest that propofol may increase QT interval, although this is likely in most cases to be clinically insignificant.

Post-operative considerations

- Following safe completion of surgery, givinostat could be re-started, typically around 72 hours post-operatively.
- Temporary interruption of treatment, even for a few weeks, is unlikely to have a clinically significant negative impact on the therapeutic effect of givinostat on muscle function in DMD.

PREGNANCY AND FERTILITY

Givinostat should not be used in pregnancy and during breast-feeding. Pre-clinical data have shown changes in reproduction.

Givinostat had no adverse effects on fertility in male and female rats but there are no data in humans.

SUPPLEMENTARY MATERIAL

Table 1S - Recommended starting dose in patients 6 years of age and older for treatment of DMD as per SmPC (Higher dose)

Weight*	Dosage	Oral Suspension Volume
10 kg to less than 20 kg	22.2 mg twice daily	2.5 mL twice daily
20 kg to less than 40 kg	31 mg twice daily	3.5 mL twice daily
40 kg to less than 60 kg	44.3 mg twice daily	5 mL twice daily
60 kg or more	53.2 mg twice daily	6 mL twice daily

**Based on actual body weight*