## Cardiac monitoring of DMD patients starting givinostat *(Duvyzat)* medication

*Link to the givinostat summary of product characteristics and patient information leaflet on the MHRA Products website:* https://products.mhra.gov.uk/search/?search=givinostat&page

**General background:**

- Very many drugs, used in the treatment of all kinds of conditions, affect cardiac repolarization. Their effects can be assessed by measuring changes in the QT-interval on a standard 12-lead ECG (eg: antibiotics, bladder stabilizing agents, anti-psychotic / anxiolytics, antihistamines, sotalol, some general anaesthetic agents, etc).
- Abnormal prolongation of the QT-interval increases the risk of serious ventricular arrhythmias such as ventricular fibrillation which, in turn can result in recurrent collapse (non-sustained VF / '*torsades de points*') or sudden cardiac death.
- Particular care is needed when prescribing / adding another drug or supplement with QT-prolonging effects for a patient already taking drugs that prolong cardiac repolarization. The combined effects of several drugs impacting QT interval can induce serious arrhythmias despite a patient being entirely stable on a single agent.
- Several online websites allow a prescriber to check whether a particular drug affects cardiac repolarization (the QT-interval).

  Some useful 'drug-checking' websites:
  - http://www.crediblemeds.org/
  - https//www.sads.org.uk/drugs-to-avoid/ *(for prescribing in inherited long-QT syndrome, but is easy to access & use for checking drug-effects on QT-interval)*

**Normal rate-corrected QT-interval (QTc) ranges by age and gender (Bazett's formula):**

Reproduced from European Cardiology Review 2017;12(2):112–20 DOI**: https://doi.org/10.15420/ecr.2017:16:1**

| QTc value (msec) | 1-15 years | Males | Females |
|---|---|---|---|
| **Normal** | <440 | <430 | <450 |
| **Borderline** | 440-460 | 430-450 | 450-470 |
| **Prolonged** | >460 | >450 | >470 |

*QTc = corrected QT. Note absence of gender difference until early adolescence. Bazett's formula adapted from Goldenberg et al., 2006*

If the automated value on the print-out appears borderline or prolonged, we recommend manual calculation of the QT interval and QTc. before prescribing a medication with potential QT-prolonging effects. Some NM specialists may be confident calculating the manual QTc themselves but most will need input from their local cardiology team.

This site (MD+CALC) provides a useful resource to support that:
https://www.mdcalc.com/calc/48/corrected-qt-interval-qtc

**It's the corrected QT-interval (QTc-interval) that you want to know and check on the ECG** - refer to *Further information on the QT-interval & the need to correct for heart rate (QTc-interval*), at the end of this document.

**Effect of givinostat on QTc-interval:**

Givinostat's effects on QTcF (Fridericia's correction) have been studied in healthy volunteers and in patients with DMD. *(NB: These studies excluded participants with QTcF >450ms, LVEF <50% or with hypokalaemia or family history of long QT syndrome).*

**The findings are mostly reassuring**:

- Givinostat does not cause clinically significant QTcF prolongation at therapeutic doses (ie: no reports >10ms increase).
- In healthy volunteers, higher doses (5 times highest approved dose) cause modest QTcF prolongation but never to >460ms and there have been no reports of arrhythmias at the time of preparing this document.

**However:**

- The givinostat label states: *Avoid concomitant use of givinostat with other product(s) with a known potential to prolong the QTc interval. If concomitant use cannot be avoided, obtain ECGs when initiating, during concomitant use, and as clinically indicated*.
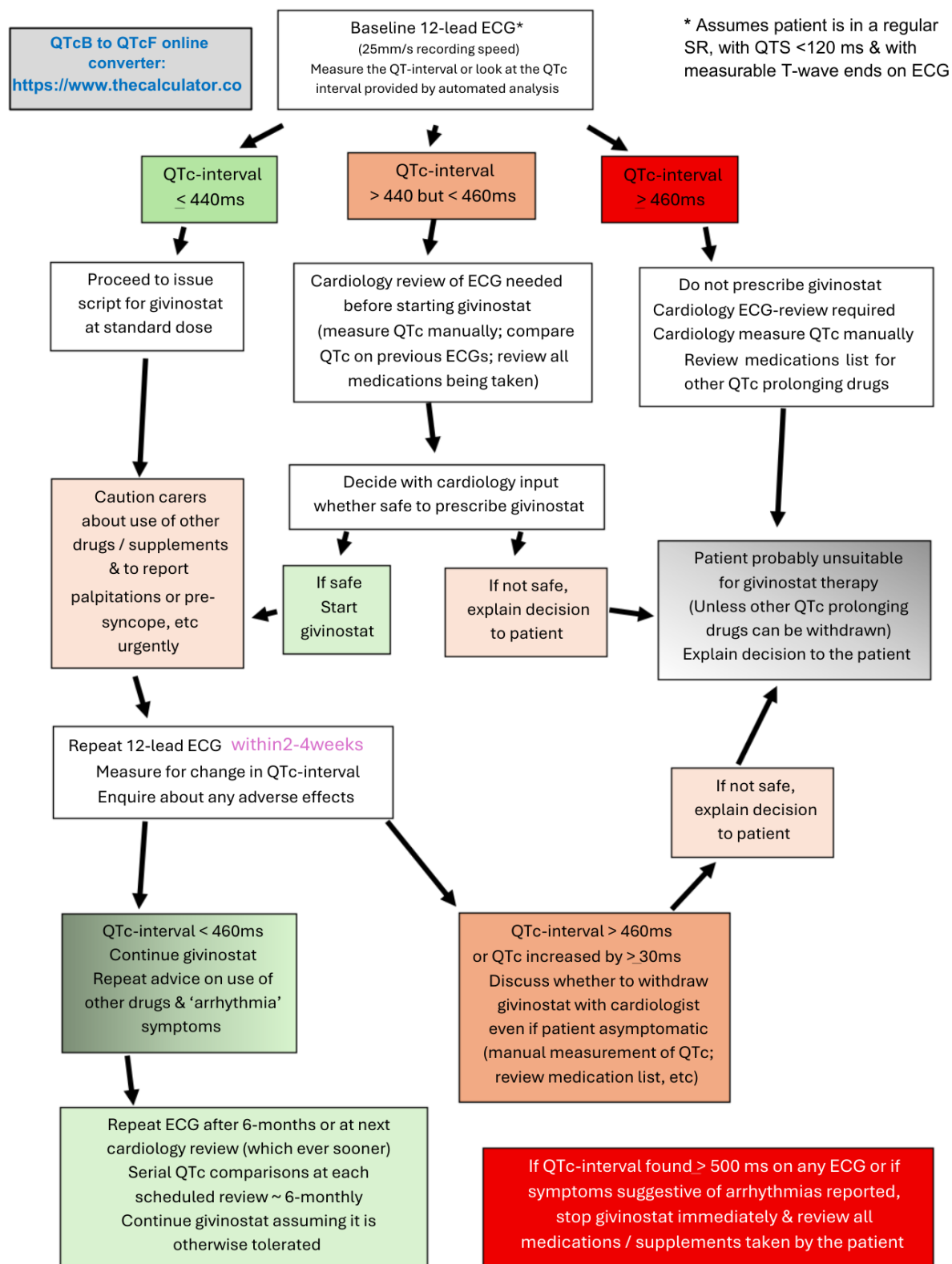-  Withhold givinostat if the QTc interval is > 500 ms or the change from baseline is > 60 ms.

**Conservative recommendation:**

- Do not start givinostat in anyone with a QTc >440ms without  discussing it with your cardiology team.
- If the manually calculated QTc is 440-460ms or if it is not possible to manually calculate the QTc then discussion with cardiology is required.
- **Caution patients / families about** the **use of any other QTc prolonging drugs** (examples of other drugs commonly used in DMD: antibiotics such as azithromycin, clarithromycin, ciprofloxacin; antiemetics such as ondansetron and anti-psychotic such as risperidone), **or over-the-counter medicines** (e.g. antihistamines such as famotidine) and of the need to make future prescribers / pharmacists aware every time they are about to prescribe / recommend anything.

- The givinostat label also specifically mentions caution using:
    o   anaesthetics (e.g. sevoflurane, propofol)
    o   class III antiarrhythmics (e.g. amiodarone, sotalol, dronedarone)
    o   an additional antibiotic (fluconazole)
    o   an additional antipsychotic (aripiprazole)


- Prescribing other drugs which can also prolong the QT-interval is <u>not</u> absolutely contraindicated in patients with DMD who are already taking givinostat. If possible,  use an alternative drug without QT-prolonging effects.  If adding another drug with QT-prolonging effects is unavoidable, close monitoring is required, with an ECG at baseline and within 2-4  weeks. Repeat ECG is also recommended/advised after dose increases and every 6 months as per givinostat guidelines.


**Planned guidance review date:**

This guidance will be reviewed within 12-months of implementation or sooner in the event of new or increased safety concerns.

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## Decision-making flow-diagram for QTc-surveillance in patients with DMD starting givinostat therapy

**QTcB to QTcF online converter:**
**https://www.thecalculator.co**

Baseline 12-lead ECG*
(25mm/s recording speed)
Measure the QT-interval or look at the QTc interval provided by automated analysis

* Assumes patient is in a regular SR, with QTS <120 ms & with measurable T-wave ends on ECG

QTc-interval
< 440ms

QTc-interval
> 440 but < 460ms

QTc-interval
> 460ms

Proceed to issue script for givinostat at standard dose

Cardiology review of ECG needed before starting givinostat (measure QTc manually; compare QTc on previous ECGs; review all medications being taken)

Do not prescribe givinostat
Cardiology ECG-review required
Cardiology measure QTc manually
Review medications list for other QTc prolonging drugs

Caution carers about use of other drugs / supplements & to report palpitations or pre-syncope, etc urgently

Decide with cardiology input whether safe to prescribe givinostat

If safe
Start givinostat

If not safe, explain decision to patient

Patient probably unsuitable for givinostat therapy (Unless other QTc prolonging drugs can be withdrawn) Explain decision to the patient

Repeat 12-lead ECG  within 2-4 weeks
Measure for change in QTc-interval
Enquire about any adverse effects

If not safe, explain decision to patient

QTc-interval < 460ms
Continue givinostat
Repeat advice on use of other drugs & 'arrhythmia' symptoms

QTc-interval > 460ms
or QTc increased by > 30ms
Discuss whether to withdraw givinostat with cardiologist even if patient asymptomatic (manual measurement of QTc; review medication list, etc)

Repeat ECG after 6-months or at next cardiology review (which ever sooner)
Serial QTc comparisons at each scheduled review ~ 6-monthly
Continue givinostat assuming it is otherwise tolerated

If QTc-interval found > 500 ms on any ECG or if symptoms suggestive of arrhythmias reported, stop givinostat immediately & review all medications / supplements taken by the patient

## Further information on the QT-interval & the need to correct for heart rate (QTc-interval)

- The QT-interval is measured from the onset of the QRS complex to the end of the T-wave on the same complex.

- The recommended lead to use for manual QT-measurement is standard lead II, but if that isn't possible, the hierarchy in descending order of leads to be used in QTc calculation is lead I & V5 or V6 .

- It may not always be possible to visualise the end of the T-wave:
  - **Refer to** Tomas Robyns (March 2024) for **'*How to: measure the QT-interval?*'** European Society of Cardiology here.

- Importantly, the actual QT-interval (ms) needs to be 'corrected' because it changes with heart rate (ie: shortens at faster and lengthens at slower heart rates).

- QTc is basically a formula to transform the recorded QT-interval to what it would be if the heart rate were 60/min.

- So, if the heart rate is 60/min, QT = QTc, no matter which correction is used (or how broad the QRS).

- There are differences in correction methods as stated – the actual formulas are:

  **Bazett's** (most commonly used clinically):   $QTc = QT\ interval\ (ms) / \sqrt{[RR\ interval\ (sec)}$

  **Fridericia's** (better at fast heart rates):   $QTc = QT\ interval / (RR\ interval)^{1/3}$ (RR = 60/heart rate)

  [ie: at relatively normal heart rates, differences between these methods will be small, at extremes of heart rate they will be significant. When the QRS-duration is prolonged > 120ms ('3 small squares') further corrections are needed to derive the QTc correctly]

- Many ECG machines provide an **automated QTc-interval (ms) measurement** – typically using Basett's formula (QTcB). However, use the automated measurement as a guide only. The machine's ability to measure a QT-interval accurately depends on several factors and so can mislead (eg: low-amplitude T-waves, prominent U-waves; etc).

- If your ECG machine does not also provide QTcF (many *will* do QTcB), you can calculate this manually, but it is strongly recommended to use this useful resource:

  https://www.mdcalc.com/calc/48/corrected-qt-interval-qtc

  or

  The Calculator*:* https://www.thecalculator.co

- **Remember, check the <u>corrected QT-interval</u> (QTc-interval) on the ECG.**

- **Refer to** Tomas Robyns (March 2024) for **'*How to: measure the QT-interval?*'** European Society of Cardiology:

  https://www.escardio.org/Councils/Council-on-Cardiovascular-Genomics/Cardiovascular-Genomics-Insight/Volume-9/how-to-measure-the-qt-interval

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