Center for Drug Evaluation and Research
Small Business and Industry Assistance
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Part 2 of 2: QTc Information in the U.S. Prescribing Information

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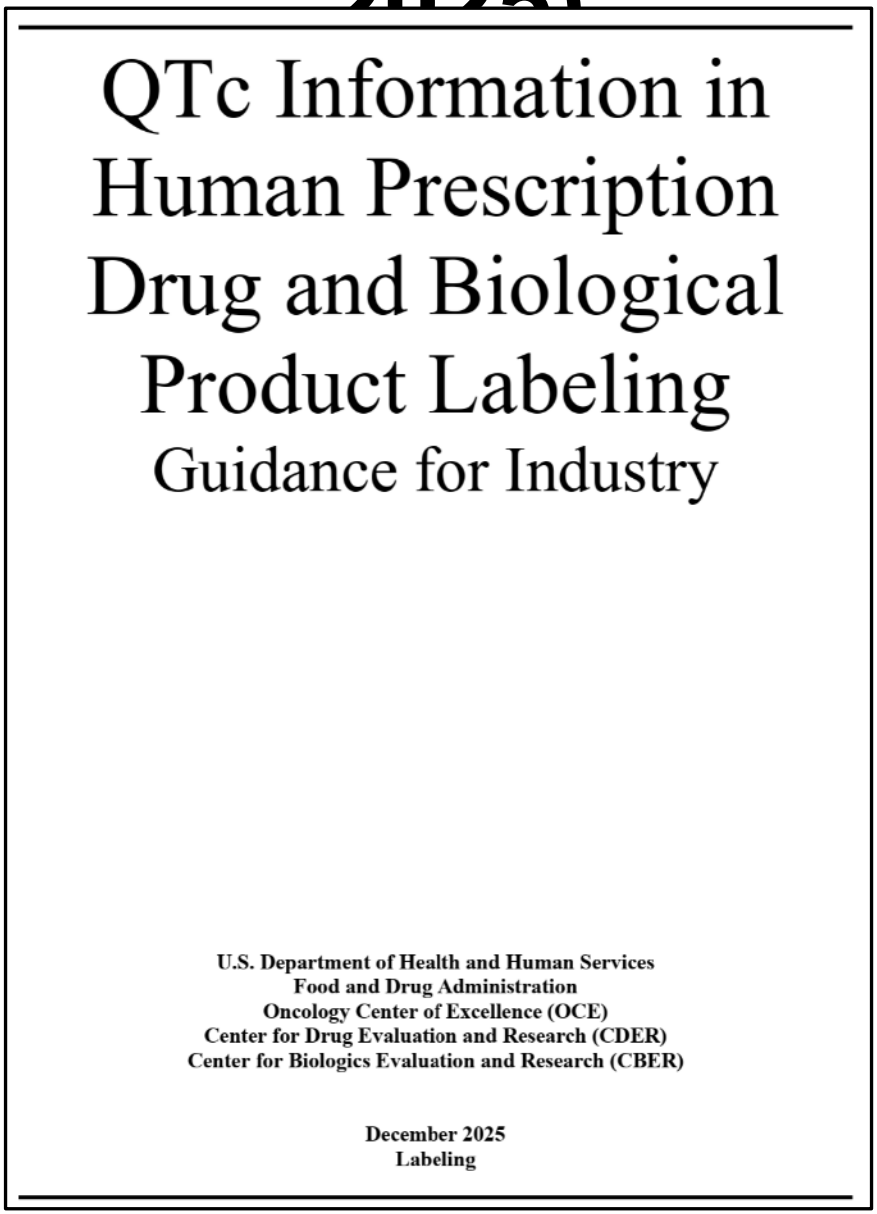
- The labeling examples in these presentations are provided only to demonstrate current labeling development challenges and should not be considered FDA recommended templates.

2025)



QTc Information in Human Prescription Drug and Biological Product Labeling

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2025
Labeling

Guidance for industry: *QTc Information in Human Prescription Drug and Biological Product Labeling* (December 2025) available at https://www.fda.gov/media/170814/download

Purpose of the QTc Interval Labeling Guidance

Objective

Assist applicants in incorporating QTc interval prolongation information into labeling for non-antiarrhythmic drugs and biological products

Key Goals

- Ensure clinically relevant QTc interval information is included
- Distribute information appropriately across labeling sections
- Comply with labeling regulatory requirements (e.g., 21 CFR 201.56 and 201.57)

QTc Prolongation Risk

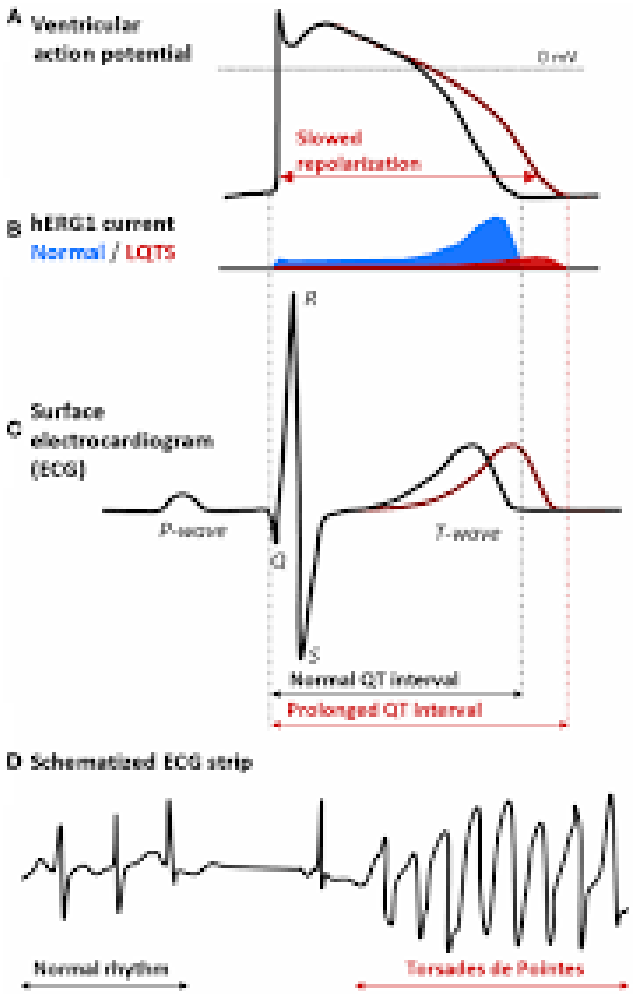


Figure from Front. Pharmacol. 1:137. doi: 10.3389/fphar.2010.00137

What is QTc Prolongation?

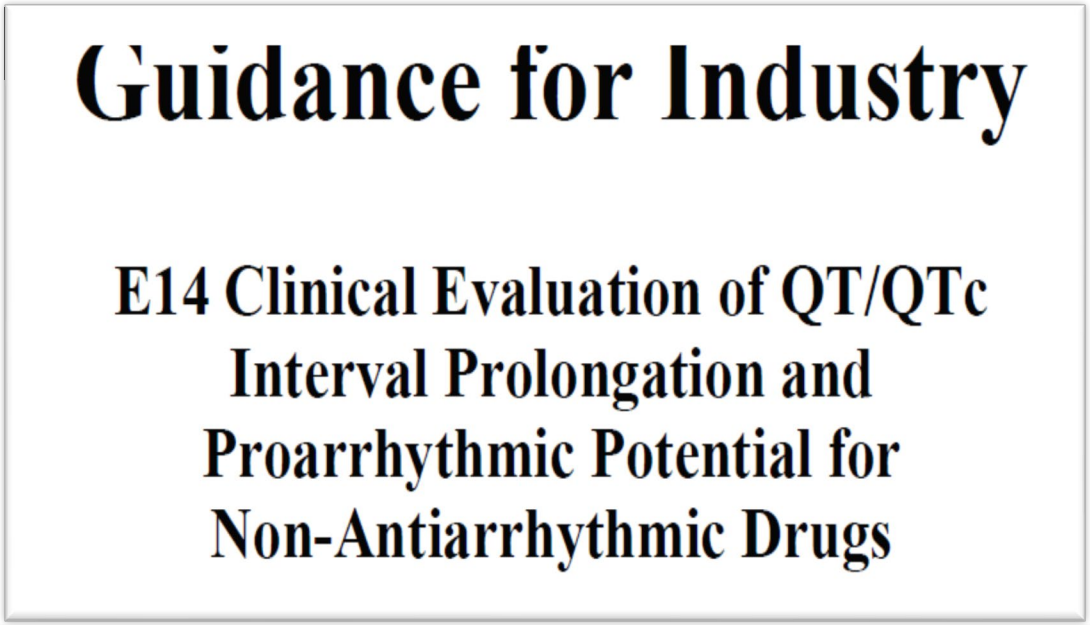
- Delay in cardiac repolarization measured on electrocardiogram (ECG)
- Creates electrophysiological environment favoring torsade de pointes (TdP)

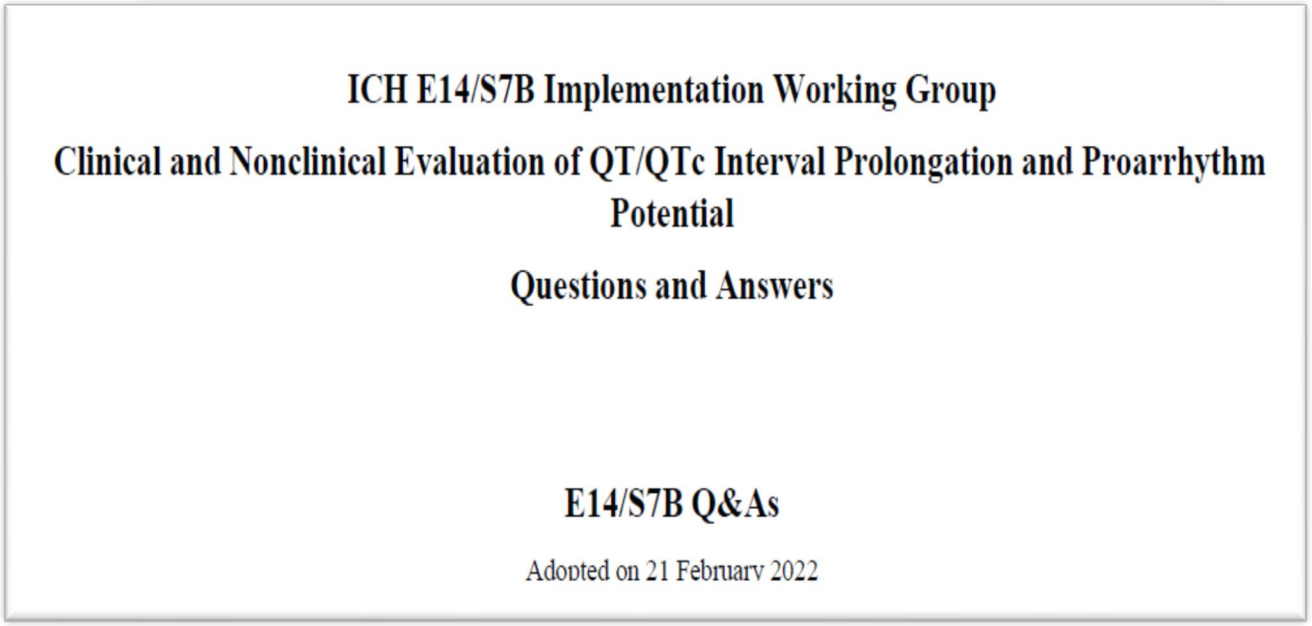
Clinical Consequences

- TdP can progress to ventricular fibrillation
- May lead to sudden death
- TdP may not be reported even in drugs with significant proarrhythmic effects

Patient Risk Factors for QTc Interval Prolongation

- Elevated baseline QTc interval
- Ischemic cardiomyopathy
- Hypokalemia
- History of long QT syndrome
- Genetic predisposition
- Concomitant use of QTc-interval-prolonging drugs
- Concomitant use of drugs that increase the exposure of the subject drug





Guidance for industry: *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (October 2005) available at https://www.fda.gov/media/71372/download https://www.fda.gov/media/170814/download

QTc Interval Assessment Strategies

FDA/ICH Recommendations

Assess cardiac repolarization effects early in clinical development for all new drugs with systemic bioavailability

Three Main Approaches

- *Thorough QT/QTc (TQT) Study:* Typically, in healthy participants with placebo, positive control, and therapeutic/supratherapeutic doses
- *Early Clinical Trials:* First-in-human or multiple-ascending dose studies with robust ECGs at sufficient exposures.
- *Integrated Nonclinical Risk Assessment:* Supplement clinical data when clinical QT/QTc studies cannot achieve sufficient exposure multiples

Cardiac Electrophysiology Heading in CLINICAL PHARMACOLOGY Section

Under Cardiac Electrophysiology heading, include:

- Studied dose(s) or observed exposure range
- Dose- or exposure-response relationship (when available)
- Effect of drug on QTc interval

12 CLINICAL PHARMACOLOGY

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12.2 Pharmacodynamics

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Cardiac Electrophysiology

The effect of DRUG-A on the QTc interval was evaluated across a dose range of 50 mg to 300 mg twice daily (2 times the highest adult approved recommended dosage) with and without strong CYP3A4 inhibitors in patients with DISEASE-A. The increase in QTc interval was **concentration dependent** with an increase in QTc predicted to be **13 msec (upper bound of 90% confidence interval: 15 msec)** at the mean steady-state maximum concentration (Cmax) observed in patients at the **highest approved recommended dosage** without strong CYP3A4 inhibitors. The increase in QTc interval was predicted to be 11 msec (upper bound of 90% confidence interval: 13 msec) at steady-state Cmax after administration **of reduced dose with strong CYP3A4 inhibitors** *[see Warnings and Precautions (5.x)].*

Cardiac Electrophysiology Heading: No Clinically Significant QTc Interval Prolongation

12 CLINICAL PHARMACOLOGY

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12.2 Pharmacodynamics

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Cardiac Electrophysiology

At 5.8 times the maximum recommended dose of DRUG-A, clinically significant QTc interval prolongation was not observed.

Cardiac Electrophysiology Heading: Insufficient Data to Characterize Affect on QTc Interval

12 CLINICAL PHARMACOLOGY

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12.2 Pharmacodynamics

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Cardiac Electrophysiology

There is insufficient information to characterize the effect of DRUG-A on the QTc interval.

May Omit Cardiac Electrophysiology Heading in Certain Situations

May omit this heading if the product has a highly localized distribution, there is no systemic absorption, or if the product is a large protein (e.g., monoclonal antibody)

12 CLINICAL PHARMACOLOGY

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12.2 Pharmacodynamics

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~~Cardiac Electrophysiology~~

QTc Interval Prolongation Information in the DRUG INTERACTIONS Section[1]

- Must include clinically significant drug interactions resulting in or increasing risk of QTc interval prolongation
- Must describe mechanism (if known)
- Must provide specific practical instructions for prevention and management
- Should include observed or predicted clinical effects

<u>Two Key Scenarios</u>

- Use of subject drug with other QTc-interval prolonging products
- Use of subject drug with products affecting the pharmacokinetics of the subject drug

[1] 21 CFR 201.57(c)(8)(i).

Use of Subject Drug With Other Products Known or Suspected to Prolong the QTc Interval

7 DRUG INTERACTIONS

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7.x Drugs that Prolong QTc Interval

Avoid concomitant use of DRUG-A with other drug(s) with known potential to prolong the QTc interval. If concomitant use cannot be avoided:

- Obtain ECGs when initiating, during concomitant use, and as clinically indicated *[see Warnings and Precautions (5.x)].*
- Withhold DRUG-A if the QTc interval is greater than 480 msec.
- Restart DRUG-A after the QTc interval returns to less than 480 msec *[see Dosage and Administration (2.x)].*

DRUG-A causes QTc interval prolongation *[see Clinical Pharmacology (12.2)].* Concomitant use of DRUG-A with other drugs that prolong the QTc interval may result in a greater increase in the QTc interval and adverse reactions associated with QTc interval prolongation *[see Warnings and Precautions (5.x)].*

Use of Subject Drug With Other Products That Affect the Pharmacokinetics of the Subject Drug

7 DRUG INTERACTIONS

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7.x Effect of Other Drugs on DRUG-A

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Strong or Moderate CYP3A4 Inducers

Avoid concomitant use of DRUG-A with strong or moderate CYP3A4 inducers.

DRUG-A is primarily metabolized by CYP3A4. Concomitant use of DRUG-A with a strong or moderate CYP3A4 inducer may decrease DRUG-A exposure (which may reduce DRUG-A effectiveness) and may increase M1 systemic exposure *[see Clinical Pharmacology (12.3)]* (which may increase the risk of QTc interval prolongation associated with elevated M1 metabolite exposure).

QTc Interval Prolongation Warning in the WARNINGS AND PRECAUTIONS Section

Include When

- QTc interval prolongation is serious or otherwise clinically significant
- Has implications for prescribing decisions or patient management

Factors Supporting Inclusion

- Clinically significant increase in proarrhythmic effects (TdP, ventricular tachycardia/fibrillation, syncope, sudden death)
- Studies demonstrate clinically significant QTc prolongation particularly when consistent with the drug's pharmacology (e.g., hERG positive at low safety margins)

Recommended Information in a QTc Interval Prolongation Warning in the W&P Section

- Description of clinically significant adverse reactions (TdP, arrhythmias, sudden death)
- Pertinent clinical trial exclusion criteria
- Percentage of patients with QTc >500 msec or >60 msec increase from baseline
- Dose/concentration relationship summary
- Risk with concomitant use of other products
- Cross-references to other sections with additional QTc interval prolongation information

Example of a QTc Interval Prolongation Warning in the W&P Section (1 of 3)

5.2 QTc Interval Prolongation and Torsades de Pointes
DRUG-A can cause QTc interval prolongation and Torsades de Pointes (TdP).

In clinical trials in Disease-X, 34% (136/400) of patients treated with DRUG-A at the recommended dosage had an QTc interval prolongation adverse reaction. Of these 136 patients, QTc interval prolongation was Grade 3 in 18% and Grade 4 in 3%. The heart-rate corrected QT interval (using Fridericia's method) (QTcF) was > 500 msec in 10% of DRUG-A-treated patients, and the increase in QTcF from baseline was > 60 msec in 24% of DRUG-A-treated patients. Dosage reduction due to QTc interval prolongation was required in 7% of DRUG-A-treated patients *[see Adverse Reactions (6.1)].* One DRUG-A-treated patient had a fatal outcome of cardiac arrest, and one patient had non-sustained TdP. Concomitant use of DRUG-A with drugs known to prolong the QTc interval may increase the risk of QTc interval prolongation [*see Drug Interactions (7.1)] …*

Example of a QTc Interval Prolongation Warning in the W&P Section (2 of 3)

5.2 QTc Interval Prolongation and Torsades de Pointes

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- Correct electrolyte abnormalities, including hypokalemia and hypomagnesemia, prior to and throughout DRUG-A treatment.
- Perform an ECG prior to initiation of DRUG-A treatment. Do not initiate DRUG-A treatment in patients with QTcF > 450 msec.
- Perform an ECG at least once a week for the first 4 weeks of DRUG-A treatment, and at least monthly thereafter. In patients with congenital long QTc syndrome, heart failure, electrolyte abnormalities, or those who are taking QTc interval prolonging drugs, more frequent ECG monitoring may be necessary ...

Example of a QTc Interval Prolongation Warning in the W&P Section (3 of 3)

5.2 QTc Interval Prolongation and Torsades de Pointes

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- Interrupt DRUG-A treatment if QTcF increases to:
  - > 480 msec and < 500 msec. If QTcF interval returns to < 480 msec, restart DRUG-A at the prior dosage.
  - > 500 msec or there is an increase in the QTcF > 60 msec from baseline. If the QTcF interval returns to < 480 msec, then restart DRUG-A at the lowest recommended dosage *[see Dosage and Administration (2.x)].*
- Permanently discontinue DRUG-A in patients with a ventricular arrhythmia and in those who develop QTc interval prolongation with signs or symptoms of a life-threatening arrhythmia.

Dosage Modifications to Reduce the Risk of QTc Interval Prolongation in the DOSAGE AND ADMINISTRATION Section

If there are recommended dosage modifications for the subject drug (e.g., dosage reduction, dosage interruption, or permanent discontinuation) to reduce the risk of QTc interval prolongation or clinically relevant adverse reactions associated with QTc interval prolongation, this information, as well as information on the recommended frequency of ECG monitoring, should be included in the DOSAGE AND ADMINISTRATION section

Example of Dosage Modifications to Reduce the Risk of QTc Interval Prolongation in the D&A Section (1 of 2)

2 DOSAGE AND ADMINISTRATION

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2.x Dosage Modifications for QTc Interval Prolongation

Perform an electrocardiogram (ECG) prior to the initiation of DRUG-A, at least once a week for the first 4 weeks, and at least monthly thereafter. See Table X for dosage modifications of DRUG-A to reduce the risk of QTc interval prolongation or clinically relevant adverse reactions associated with QTc interval prolongation …

Example of Dosage Modifications to Reduce the Risk of QTc Interval Prolongation in the D&A Section (2 of 2)

2.x Dosage Modifications for QTc Interval Prolongation

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Table X: Dosage Modifications Due to QTc Interval Prolongation or Adverse Reactions Associated with QTc Interval Prolongation

QTc interval > 480 msec and < 500 msec	• Interrupt DRUG-A. • Check electrolyte levels. Correct hypokalemia and hypomagnesemia [*see Warnings and Precautions (5.2)*]. • If the QTc interval returns to < 480 msec, restart DRUG-A at the prior dosage level
QTc interval greater than 500 msec (Grade 3) or there is an increase in the QTcF > 60 msec from baseline.	• Interrupt DRUG-A • Check electrolyte levels. Correct hypokalemia and hypomagnesemia *[see Warnings and Precautions (5.2)]*. • If the QTc interval returns to < 480 msec, restart DRUG-A at the lowest recommended dosage
QTc interval prolongation with signs/symptoms of lifethreatening arrhythmia, Torsades de pointes, polymorphic ventricular tachycardia (Grade 4)	Permantly discontinue DRUG-A

QTc Interval Prolongation in a BOXED WARNING

A boxed warning for QTc interval prolongation is recommended when there is reasonable evidence of a causal association between the drug and any of the following:

- TdP
- Polymorphic ventricular tachycardia or signs or symptoms of serious or life-threatening arrythmias
- Other life-threatening cardiac adverse reactions with QTc interval prolongation
- Extensive QTc prolongation (e.g., >20 msec) for drugs indicated in a patient population that is also at high-risk for cardiac arrhythmias
- Cardiac death with QTc interval prolongation

Example of a QTc Interval Prolongation Boxed Warning

WARNING: QTC INTERVAL PROLONGATION AND TORSADES DE POINTES

DRUG-A can cause QTc prolongation and Torsades de Pointes *[see Dosage and Administration (2.x) and Warnings and Precautions (5.x)]:*

- **Correct hypokalemia and hypomagnesemia prior to and during DRUG-A treatment.**
- **Do not initiate DRUG-A in patients with QTcF > 450 msec.**
- **Interrupt DRUG-A treatment if QTcF increases to > 480 msec**
- **Permanently discontinue DRUG-A in patients with a ventricular arrhythmia and in those who develop QTc interval prolongation with signs or symptoms of a life-threatening arrhythmia.**

Including QTc Interval Information in Other Sections

- CONTRAINDICATIONS: Consider for patients at high risk of QTc interval prolongation when risk clearly outweighs benefit
- ADVERSE REACTIONS: Must include QTc-related adverse reactions
- PATIENT COUNSELING INFORMATION: Summarize adverse reactions or risks associated with QTc interval prolongation that should be conveyed to the patient

Including QTc Interval Prolongation Information in Patient Labeling

- If a drug has clinically significant QTc interval prolongation information, the clinically significant adverse reactions or risks associated with QTc interval prolongation should generally be described in FDA-approved patient labeling (e.g., Medication Guide, Patient Package Insert)
- Describe risks in patient-friendly language
- Include signs/symptoms for patients to report (dizziness, fainting, palpitations, chest pain)

Submission Requirements

When new QTc interval prolongation-related information becomes available, applicants must submit to FDA proposed labeling in a prior approval supplement

Key Takeaways

- The December 2025 guidance provides a framework for incorporating QTc information appropriately across labeling sections
- Transparency and specificity are essential. Clearly communicate what is known and unknown about your drug's QTc effects
- Provide prescribers with actionable information: monitoring recommendations, dose modification thresholds, and management strategies
- Resources
  - 2025 guidance on "QTc Information in Human Prescription Drug and Biological Product Labeling”
  - ICH E14 and E14/S7B Q&As for QTc assessment methodology
  - Contact your review division for product-specific questions

End of Presentation