VANFLYTA®
(quizartinib) tablets

VANFLYTA (quizartinib) REMS (Risk Evaluation Mitigation Strategy) Prescriber Training Program

Reference ID: 5212288

VANFLYTA Prescriber Training Program

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- This training module provides details related to the VANFLYTA REMS requirements for Prescribers in order to prescribe VANFLYTA.
- Please refer to the Prescribing Information for additional information.

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Training Overview

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- What is a REMS?
- What is VANFLYTA?
  - Indication
  - Boxed Warning
    - **QT Prolongation, Torsades de pointes and cardiac arrest**
  - Clinical Data
- QT Prolongation Mechanism of Action: Inhibition of the Slow Delayed Rectifier Potassium Current, IKs
- What are the Risk Factors for QT Prolongation, Torsades de Pointes and Cardiac Arrest?
- What are the Risk Mitigation Strategies?
  - What do Prescribers Need to Do Before Treatment?
  - What do Prescribers Need to Do During Treatment?
  - Dosing and Administration
  - Dosing Modifications for Adverse Reactions
- How do Prescribers Become Certified in the VANFLYTA REMS?

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What is a REMS?

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- A Risk Evaluation and Mitigation Strategy (REMS) is a program required by the FDA to manage known or potential serious risks associated with a drug product. The FDA has determined that a REMS is necessary to ensure that the benefits of VANFLYTA outweigh its risks.

- The goals of the VANFLYTA REMS are to mitigate the serious risks of QT prolongation, Torsades de Pointes, and cardiac arrest by ensuring that:
  - Prescribers are able to identify the unique QT prolonging mechanism of VANFLYTA.
  - Prescribers are able to identify the risk factors that are associated with Torsades de Pointes and cardiac arrest with VANFLYTA .
  - Prescribers are able to identify the importance of providing risk mitigation measures including QTc interval monitoring, electrolyte monitoring and repletion, avoidance of concomitant QT prolonging medications, and dose modifications/dose interruptions when indicated

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What is VANFLYTA?

VANFLYTA® (quizartinib) is a kinase inhibitor indicated in combination with standard cytarabine and anthracycline induction and cytarabine consolidation, and as maintenance monotherapy following consolidation chemotherapy, for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) that is FLT3 internal tandem duplication (ITD)-positive as detected by an FDA-approved test.

Limitations of Use:

VANFLYTA is not indicated as maintenance monotherapy following allogeneic hematopoietic stem cell transplantation (HSCT); improvement in overall survival with VANFLYTA in this setting has not been demonstrated.

Contraindication:

VANFLYTA is contraindicated in patients with severe hypokalemia, severe hypomagnesemia, long QT syndrome, or in patients with a history of ventricular arrythmias or Torsades de Pointes.

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Boxed Warning: QT Prolongation, Torsades de Pointes and Cardiac Arrest

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Boxed Warning includes:

- VANFLYTA prolongs the QT interval. Prior to VANFLYTA administration and periodically, perform electrocardiograms (ECGs), monitor for hypokalemia or hypomagnesemia, and correct deficiencies.
- Torsades de pointes and cardiac arrest have occurred in patients receiving VANFLYTA. Do not administer VANFLYTA to patients with severe hypokalemia, severe hypomagnesemia, or long QT syndrome.
- Do not initiate treatment with VANFLYTA or escalate the VANFLYTA dose if **the QT interval corrected by Fridericia's formula (QTcF) is greater than 450 ms.**
- Monitor ECGs more frequently if concomitant use of drugs known to prolong the QT interval is required.
- Reduce the VANFLYTA dose when used concomitantly with strong CYP3A inhibitors, as they may increase quizartinib exposure.

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How Can Prescribers Help Mitigate The Serious Risks?

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Mechanism of Action (IKs inhibition):	Risk Factors:	Mitigation Strategies:
• The mechanism of QT interval prolongation is via inhibition of the slow delayed rectifier potassium current, I_{Ks} • All other medications that prolong the QT interval do so via the rapid delayed rectifier potassium current, $I_{kr.}$ • Inhibition of I_{Ks} and I_{Kr} may leave patients with limited reserve leading to a higher risk of QT prolongation and serious cardiac arrhythmias, including fatal outcomes	• Hypokalemia/hypomagnesemia • Concomitant QT prolonging medications • History of long QT syndrome • Uncontrolled or significant cardiovascular disease, recent myocardial infarction, heart failure, unstable angina, bradyarrhythmias, tachyarrhythmias, uncontrolled hypertension, high degree atrioventricular block, severe aortic stenosis, or uncontrolled hypothyroidism	• Strict QTc interval monitoring • Electrolyte monitoring and repletion • Avoidance of concomitant QT prolonging medications • VANFLYTA Dose interruptions/ dose modifications

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QT Prolongation with Quizartinib: Inhibition of the Slow Delayed Rectifier Potassium Current, IKs

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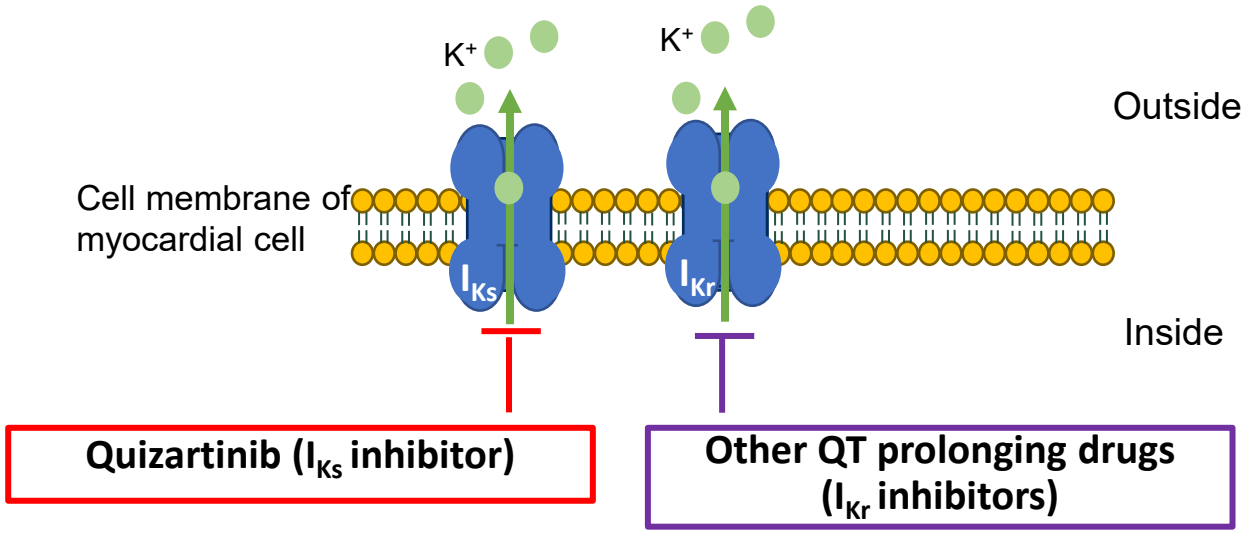
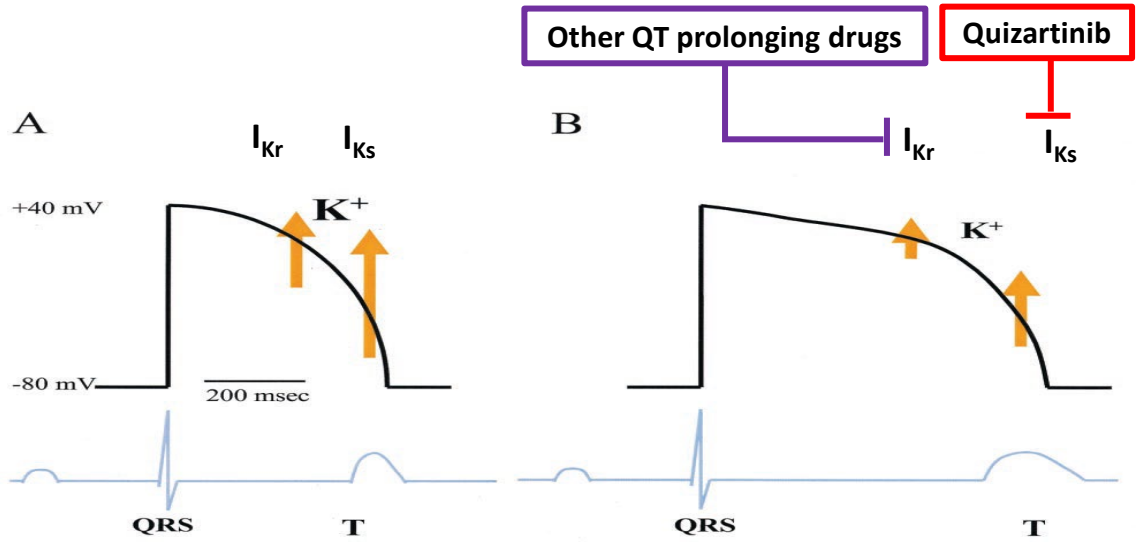
- Ventricular repolarization depends largely on the transmembrane outward transport of potassium ions via rapidly (I_{Kr}) and slowly (I_{Ks}) activating delayed rectifier potassium ion channels
- Second current provides 'repolarization reserve' when one channel is blocked
- A reduction in repolarizing current via I_{Kr} and/or I_{Ks} can prolong the QT interval, resulting in an increased risk of arrythmias





A. Repolarization via I_{Ks} and I_{Kr} in normal conditions

B. Decreased I_{Kr} and/or I_{Ks} repolarizing currents prolong the action potential

1. Adapted with permission from: Tristani-Firouzi M, Chen J, Mitcheson JS, Sanguinetti MC. Molecular biology of K(+) channels and their role in cardiac arrhythmias. Am J Med. 2001 Jan;110(1):50-9..

QT Prolonging Mechanism of Action

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- **Inhibition of the Slow Delayed Rectifier Potassium Current, IKs**
- VANFLYTA prolongs the QT interval in a dose- and concentration-related manner.
  - **The exposure-response analysis predicted a concentration-dependent QTcF interval median prolongation of 18 and 24 ms [upper bound of 2-sided 90% confidence interval (CI): 21 and 27 ms] at the median steady-state Cmax of quizartinib at the 26.5 mg and 53 mg dose level during maintenance therapy**
- The mechanism of QT interval prolongation is via inhibition of the slow delayed rectifier potassium current, I_{Ks}, as compared to all other medications that prolong the QT interval, which is via the rapid delayed rectifier potassium current, I_{Kr}.
  - Therefore, the level of QTc prolongation with VANFLYTA that predicts the risk of cardiac arrhythmias is unclear.
  - Inhibition of IK_s and IK_r may leave patients with limited reserve, leading to a higher risk of QT prolongation and serious cardiac arrhythmia, including fatal outcomes.

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Clinical Studies

- In 1,081 patients with AML treated with VANFLYTA in the clinical trials, Torsades de Pointes occurred in approximately 0.2% of patients, cardiac arrest occurred in 0.6%, including 0.4% with a fatal outcome, and 0.1% of patients experienced ventricular fibrillation. These severe cardiac arrhythmia events occurred predominantly during the induction phase.
- Of 265 patients with newly diagnosed FLT3-ITD-positive AML treated with VANFLYTA in combination with chemotherapy in a clinical trial, 2.3% were found to have a QTcF greater than 500 ms and 10% of patients had an increase from baseline QTcF greater than 60 ms.

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Risk Factors for QT Prolongation, Torsades de Pointes and Cardiac Arrest

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- Induction phase of treatment
- Hypokalemia
- Hypomagnesemia
- Concomitant QT prolonging medications
- History of long QT syndrome
- Uncontrolled or significant cardiovascular disease, recent myocardial infarction, heart failure, unstable angina, bradyarrhythmias, tachyarrhythmias, uncontrolled hypertension, high degree atrioventricular block, severe aortic stenosis, or uncontrolled hypothyroidism

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What do Prescribers Need to do Before Initiating Treatment? (1)

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- **Assess** each Patient for a history of ventricular arrhythmias or Torsades de Pointes, and electrolytes deficiencies
  - Do not use VANFLYTA in patients with severe hypokalemia, severe hypomagnesemia, long QT syndrome or in patients with a history of ventricular arrhythmias or Torsades de Pointes.
- **Perform** an electrocardiogram (ECG).
  - Do not initiate treatment with VANFLYTA if QTcF (QT interval corrected by Fridericia's formula) > 450 ms.
  - During induction and consolidation, perform an ECG prior to initiation and then once weekly during VANFLYTA treatment or more frequently as clinically indicated.
- **Monitor** for hypokalemia and hypomagnesemia and correct deficiencies.
  - Correct electrolyte abnormalities prior to initiation of treatment with VANFLYTA

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What do Prescribers Need to do Before Initiating Treatment? (2)

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- **Screen** for possible drug interactions with other drugs that prolong QT interval or strong CYP3A inhibitors and modify dosing as per the Prescribing Information.
- **Reduce** the VANFLYTA dose when used concomitantly with strong CYP3A inhibitors, as they may increase quizartinib exposure

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What do Prescribers Need to do Before Initiating Treatment? (3)

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Counsel the patient on:

- How to recognize and respond to signs and symptoms related to QT prolongation, Torsades de Pointes, and cardiac arrest.
- The need to report any symptoms suggestive of QT prolongation, Torsades de Pointes, and cardiac arrest to their healthcare provider or emergency room provider immediately
- Carrying the **Patient Wallet Card** at all times and showing to the card to all of their healthcare providers.

Complete the **Patient Wallet Card** and provide to the Patient before discharge.

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What do Prescribers Need to do During Treatment? (1)

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- During induction and consolidation, **perform** an ECG prior to initiation and then once weekly during VANFLYTA treatment or more frequently as clinically indicated.
- **During maintenance, perform** ECGs once weekly for at least the first month following dose initiation and escalation, and as clinically indicated thereafter. Do not escalate the dose if QTcF is greater than 450 ms.
- Perform ECG monitoring of the QT interval more frequently in patients who are at significant risk of developing QT interval prolongation and torsades de pointes or following dose escalation.
- **Reduce** VANFLYTA if QTcF increases to greater than 480 ms and less than 500 ms. Interrupt and reduce VANFLYTA if QTcF increases to greater than 500 ms.
- **Permanently discontinue** VANFLYTA in patients who develop recurrent QTcF greater than 500 ms or QTc interval prolongation with signs or symptoms of life-threatening arrhythmia

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What do Prescribers Need to do During Treatment? (2)

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- **Monitor** for hypokalemia and hypomagnesemia and correct deficiencies as per the Prescribing Information.
  - Maintain electrolytes in the normal range.
  - Monitor electrolytes and ECGs more frequently in patients who experience diarrhea or vomiting.
- **Screen** for possible drug interactions with other drugs that prolong QT interval or strong CYP3A inhibitors and modify dosing as per the Prescribing Information.
  - **Avoid** concomitant administration of drugs that prolong the QT interval, if possible
  - **Reduce** the VANFLYTA dose when used concomitantly with strong CYP3A inhibitors, as they may increase quizartinib exposure
  - **Monitor** ECGs more frequently if concomitant use of drugs known to prolong the QT interval is required.

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VANFLYTA Dosing and Administration

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VANFLYTA Dose Regimen

VANFLYTA Initiation	Induction*	Consolidation†	Maintenance
	Starting on Day 8 (for 7 + 3 regimen)‡	Starting on Day 6	Starting on Day 1
Dose	35.4 mg orally once daily	35.4 mg orally once daily	• Administer 26.5 mg orally once daily Days 1 through 14 of the first cycle if QTcF is less than or equal to 450 ms. • Increase the dose to 53 mg once daily on Day 15 of the first cycle if QTcF is less than or equal to 450 ms. Maintain the 26.5 mg once daily dose if QTcF greater than 500 ms was observed during induction or consolidation.
Duration (28-day cycles)	Two weeks in each cycle (Days 8 to 21)‡	Two weeks in each cycle (Days 6 to 19)	• Once daily with no break between cycles for up to 36 cycles

*Patients can receive up to 2cycles of induction.
† Patients can receive up to 4cycles of consolidation.
‡ For 5+2 regimen as the second induction cycle, VANFLYTA will be given on Days6 to 19.

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Recommended Dosage Modifications for Adverse Reactions

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Adverse Reaction	Recommended Action
QTcF between 450 ms and 480 ms (Grade 1)	• Continue VANFLYTA dose.
QTcF between 481 ms and 500 ms (Grade 2)	• Reduce the dose of VANFLYTA (see Table 1 on next slide) without interruption. • Resume VANFLYTA at the previous dose in the next cycle if QTcF has decreased to less than 450 ms. Monitor the Patient closely for QT prolongation during the first cycle at the increased dose.
QTcF greater than 500 ms (Grade 3)	• Interrupt VANFLYTA. • Resume VANFLYTA at a reduced dose (see Table 1 on next slide) when QTcF returns to less than 450 ms. • Maintain the 26.5 mg once daily dose during maintenance if QTcF greater than 500 ms was observed during induction or consolidation.
Recurrent QTcF greater than 500 ms (Grade 3)	• Permanently discontinue VANFLYTA if QTcF greater than 500 ms recurs despite appropriate dose reduction and correction/elimination of other risk factors (e.g., serum electrolyte abnormalities, concomitant QT prolonging medications).
Torsades de pointes, polymorphic ventricular tachycardia, signs/symptoms of life-threatening arrhythmia (Grade 4)	• Permanently discontinue VANFLYTA.
Grade 3 or 4 hypokalemia (<3mmol/l) or hypomagnesemia(<0.4 mmol/l or <0.9 mg/dL)	• Interrupt VANFLYTA. • Correct hypokalemia and hypomagnesemia according to institutional guidelines. • VANFLYTA may be restarted at the previous dose when the adverse reaction improves to Grade 2 or less without symptoms.

Grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03).

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VANFLYTA Dosage Modifications

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Table 1 - Recommended Dosage Adjustments for Adverse Reactions

Current Dosage	Modified Dosage
53 mg once daily	35.4 mg once daily
35.4 mg once daily	26.5 mg once daily
26.5 mg once daily	Interrupt
17.7 mg once daily	Interrupt

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In Summary: How Can Prescribers Help Mitigate The Serious Risks?

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Mechanism of Action (IKs inhibition):	Risk Factors:	**Mitigation Strategies**:
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How do Prescribers Become Certified in the VANFLYTA REMS?

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To become certified, Prescribers must:

- Review this **Prescriber Training Program** and the VANFLYTA Prescribing Information
- Successfully complete and submit the-**Knowledge Assessment** to the REMS
- Complete the **Prescriber Enrollment Form** and submit it to the REMS

Note: Pharmacies must also be certified in the REMS. Pharmacies are required to confirm that Prescribers are certified before dispensing VANFLYTA.

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Adverse Event Reporting

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- To report serious adverse events suggestive of QT prolongation, Torsades de Pointes, and cardiac arrest, or other side effects during the use of VANFLYTA, contact Daiichi Sankyo, Inc. at 1-877-4DS-PROD (1-877-437-7763) and/or to FDA at www.fda.gov/medwatch or call 1-800-FDA-1088.

- For the complete safety profile of VANFLYTA, please see the full US Prescribing Information, available at www.VANFLYTAREMS.com.

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Additional VANFLYTA REMS Information

For further information, please visit www.VANFLYTAREMS.com or call 1-855-212-6670