VANFLYTA®
quizartinib tablets
26.5 mg | 17.7 mg

The VANFLYTA REMS

A **one-time** training for: Prescribers, Pharmacies, and Wholesalers/Distributors before prescribing, dispensing, or distributing VANFLYTA*

ENROLL TODAY AT **www.VANFLYTAREMS.com**
OR BY CALLING **1-855-212-6670**

*Pharmacies: If the person designated as the Authorized Representative changes, a new representative from your organization must be trained and certified.

Important Safety Information

WARNING: QT PROLONGATION, TORSADES DE POINTES, and CARDIAC ARREST

- **VANFLYTA® (quizartinib) prolongs the QT interval in a dose- and concentration-related manner. Prior to VANFLYTA administration and periodically, monitor for hypokalemia or hypomagnesemia, and correct deficiencies. Perform electrocardiograms (ECGs) to monitor the QTc at baseline, weekly during induction and consolidation therapy, weekly for at least the first month of maintenance, and periodically thereafter.**
- **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.**
- **Because of the risk of QT prolongation, VANFLYTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the VANFLYTA REMS.**

Indication

VANFLYTA is 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.

Please see Important Safety Information and Full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

What is the VANFLYTA REMS?

REMS (Risk Evaluation and Mitigation Strategy) is a drug safety program that helps to ensure that the benefits of the medication outweigh its risks. The goals of the VANFLYTA REMS are to mitigate the serious risks of QT prolongation, torsades de pointes, and cardiac arrest through education of optimal risk mitigation strategies, including QTc interval monitoring, monitoring and correction of hypokalemia and hypomagnesemia, dose modification, and screening for drug interactions.

SEE PAGE 4 FOR REMS REQUIREMENTS FOR WHOLESALERS/DISTRIBUTORS

For Prescribers

Become certified at www.VANFLYTAREMS.com with a one-time enrollment to prescribe VANFLYTA:

1. Review the US Prescribing Information (USPI) for VANFLYTA.
2. Review the REMS Prescriber Training Program.
3. Successfully complete the Prescriber Knowledge Assessment and submit it to the REMS.
4. Enroll by completing the Prescriber Enrollment Form and submitting it to the REMS.

Before treatment initiation (first dose) with VANFLYTA:

1. 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 Prescriber or emergency room provider immediately
   - The need to carry the Patient Wallet Card at all times
2. Complete the Patient Wallet Card and provide the Patient Wallet Card to the Patient.

During treatment:

Report serious adverse events suggestive of QT prolongation, torsades de pointes, and cardiac arrest to Daiichi Sankyo, Inc.

Important Safety Information

Contraindications

VANFLYTA is contraindicated in patients with severe hypokalemia, severe hypomagnesemia, long QT syndrome, or in patients with a history of ventricular arrhythmias or torsades de pointes.

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For Pharmacies

Become certified to dispense at www.VANFLYTAREMS.com:

1. Designate an Authorized Representative to carry out the certification process and oversee implementation and compliance with the VANFLYTA REMS requirements on behalf of the Pharmacy.
2. Have the Authorized Representative enroll by completing the Pharmacy Enrollment Form and submitting it to the REMS at www.VANFLYTAREMS.com.
3. Train all relevant staff involved in dispensing VANFLYTA on the REMS requirements prior to dispensing.
4. Establish processes and procedures to verify the Prescriber is certified.
5. If the Authorized Representative changes, the new Authorized Representative must enroll in the REMS by completing the Pharmacy Enrollment Form.

Before dispensing:

Verify the Prescriber is certified through the processes and procedures established as a requirement of the REMS.

At all times:

1. Report serious adverse events suggestive of QT prolongation, torsades de pointes, and cardiac arrest to Daiichi Sankyo, Inc.
2. Do not distribute, transfer, loan, or sell VANFLYTA except to certified Pharmacies.
3. Maintain records that processes and procedures are in place and are being followed.
4. Maintain records of all VANFLYTA dispenses and provide data to the REMS.
5. Comply with audits to ensure that all training, processes, and procedures are in place and are being followed.

Important Safety Information

Warnings and Precautions

QT Prolongation, Torsades de Pointes, and Cardiac Arrest (See BOXED WARNING)

VANFLYTA prolongs the QT interval in a dose- and concentration-dependent manner. The mechanism of QTc interval prolongation is via inhibition of the slow delayed rectifier potassium current, I_{Ks}, as compared to all other medications that prolong the QTc interval, which is via the rapid delayed rectifier potassium current, I_{Kr}.

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For Wholesalers/Distributors

To be able to distribute:

1. Establish processes and procedures to ensure that VANFLYTA is distributed only to certified Pharmacies.
2. Train all relevant staff involved in distribution on the REMS requirements.
3. Distribute VANFLYTA only to certified Pharmacies.
4. Maintain records that all processes and procedures are in place and are being followed.
5. Maintain records of drug distribution and provide these records to the REMS at specified intervals.
6. Comply with audits to ensure that all processes and procedures are in place and are being followed.

SEE PAGES 2-3 FOR THE REMS REQUIREMENTS FOR PRESCRIBERS AND FOR PHARMACIES

Enroll in the REMS today to ensure you can prescribe VANFLYTA

For more information and to enroll, visit **www.VANFLYTAREMS.com** or call the REMS Coordinating Center at **1-855-212-6670**

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- Reduce the VANFLYTA dose when used concomitantly with strong CYP3A inhibitors, as they may increase quizartinib exposure.
- Because of the risk of QT prolongation, VANFLYTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the VANFLYTA REMS.

To report SUSPECTED ADVERSE REACTIONS, contact Daiichi Sankyo, Inc, at 1-877-437-7763 or the FDA at 1-800-FDA-1088 or fda.gov/medwatch.

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Warnings and Precautions

QT Prolongation, Torsades de Pointes, and Cardiac Arrest (See BOXED WARNING)
VANFLYTA prolongs the QT interval in a dose- and concentration-dependent manner. The mechanism of QTc interval prolongation is via inhibition of the slow delayed rectifier potassium current, I_{Ks}, as compared to all other medications that prolong the QTc 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 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. Torsades de pointes, ventricular fibrillation, cardiac arrest, and sudden death have occurred in patients treated with VANFLYTA.

Of the 1,081 patients with AML treated with VANFLYTA in clinical trials, torsades de pointes occurred in approximately 0.2% of patients, cardiac arrest occurred in 0.6% of patients, including 0.4% with a fatal outcome, and 0.1% of patients experienced ventricular fibrillation. These severe cardiac arrhythmias occurred predominantly during the induction phase.

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Important Safety Information (cont.)

Warnings and Precautions (cont.)

Of the 265 patients with newly diagnosed FLT3-ITD–positive AML treated with VANFLYTA in combination with chemotherapy in the 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. The clinical trial excluded patients with a QTcF ≥450 ms or other factors that increased the risk of QT prolongation or arrhythmic events (eg, NYHA Class III or IV congestive heart failure, hypokalemia, family history of long QT interval syndrome).

Therefore, avoid use in patients who are at significant risk of developing torsades de pointes, including uncontrolled or significant cardiac disease, recent myocardial infarction, heart failure, unstable angina, bradyarrhythmias, tachyarrhythmias, uncontrolled hypertension, high-degree atrioventricular block, severe aortic stenosis, or uncontrolled hypothyroidism.

Do not initiate treatment with VANFLYTA if the QTcF interval is greater than 450 ms. 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 ECG and correct electrolyte abnormalities prior to initiation of treatment with VANFLYTA.

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 prior to initiation, 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.

Monitor and correct hypokalemia and hypomagnesemia prior to and during treatment with VANFLYTA. Maintain electrolytes in the normal range. Monitor electrolytes and ECGs more frequently in patients who experience diarrhea or vomiting. Monitor patients more frequently with ECGs if coadministration of VANFLYTA with 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. Reduce VANFLYTA if QTc increases to greater than 480 ms and less than 500 ms. Interrupt and reduce VANFLYTA if QTc increases to greater than 500 ms. Permanently discontinue VANFLYTA in patients who develop recurrent QTc greater than 500 ms or QTc interval prolongation with signs or symptoms of life-threatening arrhythmia. VANFLYTA is available only through a restricted program under a REMS.

VANFLYTA REMS

VANFLYTA is available only through a restricted distribution program under a REMS called the VANFLYTA REMS because of the serious risk of QT prolongation, torsades de pointes, and cardiac arrest.

Notable requirements of the VANFLYTA REMS include the following:

- Prescribers must be certified in the VANFLYTA REMS by enrolling and completing training.
- Prescribers must counsel patients receiving VANFLYTA about the risk of QT prolongation, torsades de pointes, and cardiac arrest, and provide patients with a Patient Wallet Card.
- Pharmacies that dispense VANFLYTA must be certified with the VANFLYTA REMS and must verify prescribers are certified through the VANFLYTA REMS.

Further information about the VANFLYTA REMS is available at www.VANFLYTAREMS.com or by telephone at 1-855-212-6670.

Embryo-Fetal Toxicity

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with VANFLYTA and for 7 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with VANFLYTA and for 4 months after the last dose.

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Important Safety Information (cont.)

Adverse Reactions

The safety of VANFLYTA (35.4 mg orally once daily with chemotherapy, 26.5 mg to 53 mg orally once daily as maintenance) in adult patients with newly diagnosed FLT3-ITD positive AML is based on QuANTUM-First.

Serious adverse reactions in ≥5% of patients who received VANFLYTA plus chemotherapy were: febrile neutropenia (11%). Fatal adverse reactions occurred in 10% of patients who received VANFLYTA plus chemotherapy, including sepsis (5%), fungal infections (0.8%), brain edema (0.8%), and one case each of febrile neutropenia, pneumonia, cerebral infarction, acute respiratory distress syndrome, pulmonary embolism, ventricular dysfunction, and cardiac arrest.

Permanent discontinuation due to an adverse reaction in patients in the VANFLYTA plus chemotherapy arm occurred in 20% of patients. The most frequent (≥2%) adverse reaction which resulted in permanent discontinuation in the VANFLYTA arm was sepsis (5%).

Dosage interruptions of VANFLYTA due to an adverse reaction occurred in 34% of patients. Adverse reactions which required dosage interruption in ≥2% of patients in the VANFLYTA arm included neutropenia (11%), thrombocytopenia (5%), and myelosuppression (3%).

Dose reductions of VANFLYTA due to an adverse reaction occurred in 19% of patients. Adverse reactions which required dosage reductions in ≥2% of patients in the VANFLYTA arm were neutropenia (9%), thrombocytopenia (5%), and electrocardiogram QT prolonged (4%).

The most common adverse reactions (≥10% with a difference between arms of ≥2% compared to placebo), including laboratory abnormalities, were decreased lymphocytes, decreased potassium, decreased albumin, decreased phosphorus, increased alkaline phosphatase, decreased magnesium, febrile neutropenia, diarrhea, mucositis, nausea, decreased calcium, abdominal pain, sepsis, neutropenia, headache, increased creatine phosphokinase, vomiting, upper respiratory tract infections, hypertransaminasemia, thrombocytopenia, decreased appetite, fungal infections, epistaxis, increased potassium, herpesvirus infections, insomnia, QT prolongation, increased magnesium, increased sodium, dyspepsia, anemia, and eye irritation.

Drug Interactions

Strong CYP3A Inhibitors

VANFLYTA is a CYP3A substrate. Concomitant use of VANFLYTA with a strong CYP3A inhibitor increases quizartinib systemic exposure, which may increase the risk of VANFLYTA adverse reactions. Reduce the dosage of VANFLYTA.

Strong or Moderate CYP3A Inducers

Concomitant use of VANFLYTA with strong or moderate CYP3A inducers decreases quizartinib systemic exposure, which may reduce VANFLYTA efficacy. Avoid concomitant use of VANFLYTA with strong or moderate CYP3A inducers.

QT Interval–Prolonging Drugs

VANFLYTA prolongs the QT/QTc interval. Coadministration of VANFLYTA with other drugs that prolong the QT interval may further increase the incidence of QT prolongation. Monitor patients more frequently with ECG if coadministration of VANFLYTA with drugs known to prolong the QT interval is required.

Use in Specific Populations

Pregnancy

VANFLYTA can cause embryo-fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus.

Lactation

Advise women not to breastfeed during treatment with VANFLYTA and for one month after the last dose.

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Important Safety Information (cont.)

Use in Specific Populations (cont.)

Females and Males of Reproductive Potential
Pregnancy Testing
Verify pregnancy status in females of reproductive potential within 7 days before starting treatment with VANFLYTA.

Contraception
Females
Advise female patients of reproductive potential to use effective contraception during treatment with VANFLYTA and for 7 months after the last dose.
Males
Advise male patients with female partners of reproductive potential to use effective contraception during treatment with VANFLYTA and for 4 months after the last dose.

Infertility
Females
Based on findings from animal studies, VANFLYTA may impair female fertility. These effects on fertility were reversible.
Males
Based on findings from animal studies, VANFLYTA may impair male fertility. These effects on fertility were reversible.

Pediatric Use
Safety and effectiveness of VANFLYTA have not been established in pediatric patients.

Geriatric Use
No overall differences in safety or efficacy were observed between patients 65 years of age and older and younger adult patients.

Renal Impairment
No dosage adjustment is recommended in patients with mild to moderate renal impairment (CLcr 30 to 89 mL/min). VANFLYTA has not been studied in patients with severe renal impairment (CLcr <30 mL/min).

Hepatic Impairment
No dosage adjustment is recommended in patients with mild hepatic impairment or moderate hepatic impairment. VANFLYTA has not been studied in patients with severe hepatic impairment.

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