IMPORTANT INFORMATION FOR HEALTHCARE PROFESSIONALS ABOUT SERIOUS RISKS ASSOCIATED WITH VANFLYTA

VANFLYTA▼

Quizartinib dihydrochloride
(Protein kinase inhibitor)

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare Professionals are asked to report any suspected adverse reactions.

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Daiichi-Sankyo

This brochure focuses on a specific adverse reaction to VANFLYTA: Serious Adverse Drug Reactions Related to QTc Interval Prolongation.

- VANFLYTA is associated with QT interval prolongation. QT interval prolongation may increase the risk of ventricular arrhythmias or torsade de pointes. In the pivotal Phase 3 clinical study, two (0.8%) patients treated with VANFLYTA experienced cardiac arrest with recorded ventricular fibrillation, one with a fatal outcome, both in the setting of severe hypokalaemia.

- VANFLYTA must not be used in patients with congenital long QT syndrome.

- VANFLYTA should be used with caution in patients who are at significant risk of developing QT interval prolongation, including patients with uncontrolled or significant cardiovascular disease (e.g., history of second-or third-degree heart block (without pacemaker), myocardial infarction within 6 months, uncontrolled angina pectoris, uncontrolled hypertension, congestive heart failure, history of clinically relevant ventricular arrhythmias or torsade de pointes, and patients receiving concomitant medicinal products known to prolong the QT interval).

- ECGs should be performed, and electrolyte abnormalities should be corrected prior to initiation of treatment.

- Do not start treatment with VANFLYTA if the QT interval corrected by Fridericia's formula (QTcF) is greater than 450 ms.

- Permanently discontinue VANFLYTA in patients who develop QT interval prolongation with signs or symptoms of life threatening arrhythmia.

STARTING VANFLYTA

VANFLYTA should be initiated only if QTcF is ≤ 450 ms.

Table 1: Dose regimen

VANFLYTA initiation	Induction [a]	Consolidation [b]	Maintenance
	Starting on day 8 (For 7 + 3 regimen)[c]	Starting on day 6	First day of maintenance therapy
Dose	35.4 mg once daily	35.4 mg once daily	• Starting dose of 26.5 mg once daily for two weeks if QTcF is ≤ 450 ms. • After two weeks, if QTcF is ≤ 450 ms, the dose should be increased to 53 mg once daily
Duration (28-day cycles)	Two weeks in each cycle	Two weeks in each cycle	Once daily with no break between cycles for up to 36 cycles.

a Patients can receive up to 2 cycles of induction.
b Patients can receive up to 4 cycles of consolidation.
c For 5 + 2 regimen as the second induction cycle, VANFLYTA will be started on Day 6.

Table 2: Recommended dose modifications for QTcF prolongation on ECG

QTcF Interval on ECG		Recommended action
Grade 1	**QTcF 450-480 ms**	Continue VANFLYTA dose.
Grade 2	**QTcF 481-500 ms**	• Reduce VANFLYTA dose (see **Table 3**) without interruption. • Resume VANFLYTA at the previous dose in the next cycle if QTcF has decreased to < 450 ms. • Monitor the patient closely for QT prolongation for the first cycle at the increased dose.
Grade 3	**QTcF ≥ 501 ms**	• Interrupt VANFLYTA. • Resume VANFLYTA at a reduced dose (see **Table 3**) when QTcF returns to < 450 ms. • Do not escalate to 53 mg once daily during maintenance if QTcF > 500 ms was observed during induction and/or consolidation, and it is suspected to be associated with VANFLYTA. • Maintain the 26.5 mg once daily dose.
	Recurrent QTcF ≥ 501 ms	Permanently discontinue VANFLYTA if QTcF > 500 ms recurs despite appropriate dose reduction and correction/elimination of other risk factors (e.g., serum electrolyte abnormalities, concomitant QT prolonging medicinal products).
Grade 4	**Torsade de pointes; polymorphic ventricular tachycardia; signs/ symptoms of life-threatening arrhythmia**	Permanently discontinue VANFLYTA.

Graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03).

Dose modifications for adverse reactions and/or concomitant medications during VANFLYTA treatment

Table 3: Dose adjustments by phase for adverse reactions and/or concomitant use with strong CYP3A inhibitors during treatment with VANFLYTA

Phase of treatment	Full dose	Dose Reductions		
		Adverse reaction	Concomitant strong CYP3A inhibitors	Adverse reaction and concomitant strong CYP3A inhibitors
Induction or Consolidation	**35.4 mg**	**26.5 mg**	**17.7 mg**	**Interrupt**
Maintenance (first two weeks)	**26.5 mg**	**Interrupt**	**17.7 mg**	**Interrupt**
Maintenance (after two weeks)	**53 mg**	**35.4 mg**	**26.5 mg**	**17.7 mg**

Concomitant use of Strong CYP3A inhibitors

- Concomitant use with strong cytochrome P450 enzyme 3A (CYP3A) inhibitors may increase quizartinib exposure.
- If concomitant use of a strong CYP3A inhibitor is unavoidable (such as **ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, nefazodone, telithromycin, grapefruit juice, and many antiretroviral medicinal products**), the dose of VANFLYTA should be reduced as shown in **Table 3**.
- After discontinuation of the strong CYP3A inhibitor, VANFLYTA should be resumed at the original dose.

Electrolyte abnormalities

Monitoring and correction of hypokalaemia and hypomagnesaemia should be performed prior to and during treatment with VANFLYTA. More frequent monitoring of electrolytes and ECGs should be performed in patients who experience diarrhoea or vomiting.

ECG Monitoring

- During induction and consolidation, ECGs should be performed prior to initiation and then once weekly during quizartinib treatment or more frequently as clinically indicated.
- During maintenance, ECGs should be performed prior to initiation and then once weekly for the first month following dose initiation and escalation, and thereafter as clinically indicated. The maintenance starting dose should not be escalated if the QTcF interval is greater than 450 ms (see **Table 1**).
- ECG monitoring of the QT interval should be performed more frequently in patients who are at significant risk of developing QT interval prolongation and torsades de pointes.
- Patients should be monitored more frequently with ECG if co-administration of VANFLYTA with medicinal products known to prolong the QT interval is required. Examples of QT prolonging medicinal products include but are not limited to antifungal azoles, ondansetron, granisetron, azithromycin, pentamidine, doxycycline, moxifloxacin, atovaquone, prochlorperazine, and tacrolimus.

Please ensure that every patient prescribed VANFLYTA has received and read the Patient Card which is provided with every pack of VANFLYTA.

Product information

For comprehensive up to date product information please see the Summary of Product Characteristics (SmPC) which is available at https://www.medicines.ie.

Adverse events should be reported.

Reporting suspected adverse drug reactions (ADRs)

- VANFLYTA ▼ is subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the HPRA Pharmacovigilance Website: **www.hpra.ie**.
- Alternatively, please report any suspected adverse reactions to Daiichi Sankyo Ireland Pharmacovigilance by email to **pharmacovigilance_ie@daiichisankyo.com** or by phone on **+353 1 489 3000**.

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